Kathleen Fuller

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SEARCH REQUEST FORM

Date: 3/21/00 Requester's Full Name: Kathleen Fuller Examiner # : 72624
Art Unit: 1614 Phone (308) 4724 Serial Number: 09/460920
Results Format Preferred (circle): PAPER DISK E-MAIL

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

SCIENTIFIC REFERENCE BR
Sci. & Tech. Info. Ctr
MAR 27
Pat. & T.M. Office

Title of Invention:

Inventors (please provide full names): Both Anne Piper

Earliest Priority Date: 12/14/99

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known.

**For Sequence Searches Only* Please include all pertinent information (parent, grandchild, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search use of metformin to treat diabetes
a close range
(2) use + dose of glyburide + to diabetes
range
3) Claim 1.
4) Claim 35
5) Claim 36
6) particle size of metformin + glyburide

Thanks
Rebecca

****

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Searcher: K Fuller
Searcher Phone #: 308-4290
Searcher Location:
Date Searcher Picked Up:
Date Completed: 3/29/00
Searcher Prep & Review Time: 20
Online Time: 80

Type of Search
___ NA Sequence (#)
___ AA Sequence (#)
___ Structure (#)
✓ Bibliographic
___ Litigation
___ Fulltext
___ Other

Vendors and Cost

=> file reg

FILE 'REGISTRY' ENTERED AT 11:33:53 ON 29 MAR 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES: 28 MAR 2000 HIGHEST RN 260273-98-1
DICTIONARY FILE UPDATES: 28 MAR 2000 HIGHEST RN 260273-98-1

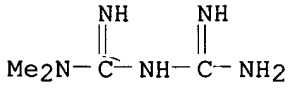
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> d l1 1-2

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 1115-70-4 REGISTRY
CN Imidodicarbonimidic diamide, N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Biguanide, 1,1-dimethyl-, hydrochloride (6CI)
CN Biguanide, 1,1-dimethyl-, monohydrochloride (8CI)
OTHER NAMES:
CN 1,1-Dimethylbiguanide hydrochloride
CN Diabefagos
CN Glucophage
CN Glyformin
CN LA 6023
CN Meguan
CN **Metformin hydrochloride**
CN N,N-Dimethylbiguanide hydrochloride
CN N1,N1-Dimethylbiguanide hydrochloride
DR 15537-72-1
MF C4 H11 N5 . Cl H
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DRUGUPDATES, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MRCK*, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (657-24-9)

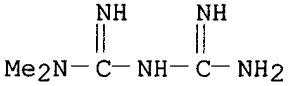


● HCl

102 REFERENCES IN FILE CA (1967 TO DATE)

102 REFERENCES IN FILE CAPLUS (1967 TO DATE)
9 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

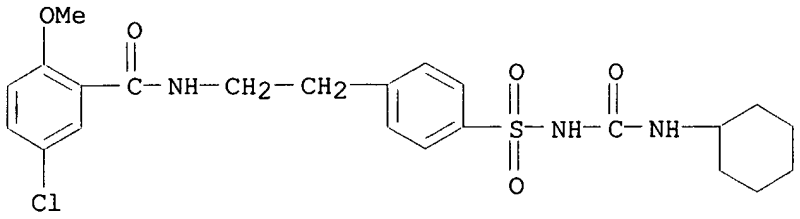
L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 657-24-9 REGISTRY
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Biguanide, 1,1-dimethyl- (6CI, 8CI)
OTHER NAMES:
CN 1,1-Dimethylbiguanide
CN Diabetosan
CN Diabex
CN Dimethylbiguanide
CN DMGG
CN Fluamine
CN Flumamine
CN Gliguanid
CN Haurymelin
CN Melbin
CN **Metformin** ✓
CN Metiguanide
CN N,N-Dimethylbiguanide
CN N,N-Dimethyldiguanide
CN N1,N1-Dimethylbiguanide
CN NNDG
FS 3D CONCORD
MF C4 H11 N5
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, DDFU, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



639 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
642 REFERENCES IN FILE CAPLUS (1967 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d l2 1-2

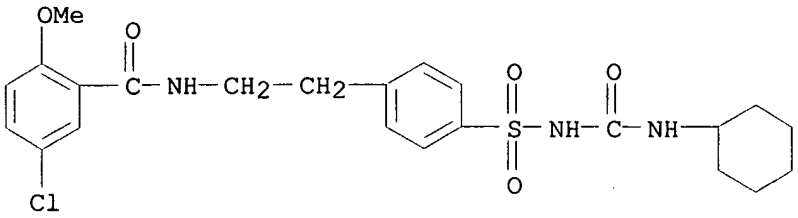
L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 23047-14-5 REGISTRY
CN Benzamide, 5-chloro-N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-2-methoxy-, potassium salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Urea, 1-[[p-[2-(5-chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexyl-, potassium salt (8CI)
OTHER NAMES:
CN **Glyburide, potassium salt** ✓
MF C23 H28 Cl N3 O5 S . x K
LC STN Files: CA, CAPLUS, TOXLIT
CRN (10238-21-8)



● x K

4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN 10238-21-8 REGISTRY
CN Benzamide, 5-chloro-N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-2-methoxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Urea, 1-[[p-[2-(5-chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexyl- (8CI)
OTHER NAMES:
CN Betanase
CN Betanaz
CN Daonil
CN Daonil N
CN Diabeta
CN Euglucan
CN Euglucon
CN Euglucon 5
CN Euglykon
CN Gilemal
CN Glibenclamide
CN Glybenzcyclamide
CN **Glyburide**
CN Glycolande N
CN HB 419
CN HD 419
CN Maninil
CN Semi-Euglucon
CN Semi-Euglucon N
CN U 26452
CN UR 606
FS 3D CONCORD
MF C23 H28 Cl N3 O5 S
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



1919 REFERENCES IN FILE CA (1967 TO DATE)
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1921 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 13:39:05 ON 29 MAR 2000
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FILE COVERS 1967 - 29 Mar 2000 VOL 132 ISS 14
FILE LAST UPDATED: 28 Mar 2000 (20000328/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d que l28

L1	2	SEA FILE=REGISTRY ABB=ON	(METFORMIN/CN OR "METFORMIN HYDROCHLORIDE"/CN)
L2	2	SEA FILE=REGISTRY ABB=ON	(GLYBURIDE/CN OR "GLYBURIDE, POTASSIUM SALT"/CN)
L3	740	SEA FILE=HCAPLUS ABB=ON	L1
L4	1928	SEA FILE=HCAPLUS ABB=ON	L2
L5	259	SEA FILE=HCAPLUS ABB=ON	L3 AND DIABETES?
L6	67	SEA FILE=HCAPLUS ABB=ON	L5 AND (DOS? OR DOSAGE?)
L7	2	SEA FILE=HCAPLUS ABB=ON	L6 AND 800
L8	11	SEA FILE=HCAPLUS ABB=ON	L5 AND (DOSE? OR DOSAGE?)(5A)LOW?
L9	9	SEA FILE=HCAPLUS ABB=ON	L6 AND (1/5 OR ONE(W)FIFTH OR 1(W)5)
L10	0	SEA FILE=HCAPLUS ABB=ON	L6 AND FIFTH
L11	8	SEA FILE=HCAPLUS ABB=ON	L6 AND (RANG? OR RATIO)
L12	27	SEA FILE=HCAPLUS ABB=ON	(L7 OR L8 OR L9 OR L10 OR L11)
L13	364	SEA FILE=HCAPLUS ABB=ON	L4 AND DIABETES
L14	105	SEA FILE=HCAPLUS ABB=ON	L13 AND (DOSE? OR DOSAGE?)
L15	13	SEA FILE=HCAPLUS ABB=ON	L14 AND (RANG? OR RATIO)
L16	16	SEA FILE=HCAPLUS ABB=ON	L13 AND (DOSE? OR DOSAGE?)(5A)LOW?
L17	5	SEA FILE=HCAPLUS ABB=ON	L13 AND (DOSE? OR DOSAGE?)(5A)REDUC?
L18	6	SEA FILE=HCAPLUS ABB=ON	L6 AND (DOSE? OR DOSAGE?)(5A)REDUC?
L19	57	SEA FILE=HCAPLUS ABB=ON	L12 OR (L15 OR L16 OR L17 OR L18)
L21	32	SEA FILE=HCAPLUS ABB=ON	L3 AND L4 AND (COMBIN? OR COMPOS?)

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L22          24 SEA FILE=HCAPLUS ABB=ON  L21 AND DIABETES
L23          19 SEA FILE=HCAPLUS ABB=ON  L22 AND (THU/RL OR PHARMACE?/SC,SX,AB,
                BI)
L24          36 SEA FILE=HCAPLUS ABB=ON  L19 AND (THU/RL OR PHARMACE?/SC,SX,AB,
                BI)
L27          26 SEA FILE=HCAPLUS ABB=ON  L19 AND THERAP?
L28          58 SEA FILE=HCAPLUS ABB=ON  L23 OR L24 OR L27


=> file wpids

FILE 'WPIDS' ENTERED AT 13:39:20 ON 29 MAR 2000
COPYRIGHT (C) 2000 DERWENT INFORMATION LTD

FILE LAST UPDATED: 23 MAR 2000              <20000323/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK            200015   <200015/DW>
DERWENT WEEK FOR CHEMICAL CODING:   200015
DERWENT WEEK FOR POLYMER INDEXING:  200015
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> D COST AND SET NOTICE DO NOT REFLECT SUBSCRIBER DISCOUNTS -
                                              SEE HELP COST <<<

>>> FOR UP-TO-DATE INFORMATION ABOUT ALL 'NEW CONTENT' CHANGES TO
    WPIDS, INCLUDING THE DERWENT CHEMISTRY RESOURCE (DCR),
    PLEASE VISIT http://www.derwent.com/newcontent.html  <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/covcodes.html  <<<

=> d que l35

L29          43 SEA FILE=WPIDS ABB=ON  R14399/DCN OR METFORMIN OR MELBIN OR
                GLUCOPHAGE OR GLYFORMIN OR MEGUAN OR GLIGUANID OR FLUAMINE OR
                FLUMANMINE
L30          88 SEA FILE=WPIDS ABB=ON  R04288/DCN OR GLYBURIDE OR GLIBENCLAMIDE

L31          73 SEA FILE=WPIDS ABB=ON  (L29 OR L30) AND ?DIABET?
L32           2 SEA FILE=WPIDS ABB=ON  L31 AND (DOSE? OR DOSAGE?)(3A)(LOW? OR
                REDUC?)
L33          10 SEA FILE=WPIDS ABB=ON  L31 AND (RANG? OR RATIO?)
L34          11 SEA FILE=WPIDS ABB=ON  L29 AND L30
L35          20 SEA FILE=WPIDS ABB=ON  (L32 OR L33 OR L34)


=> file medline

FILE 'MEDLINE' ENTERED AT 13:39:33 ON 29 MAR 2000

 FILE LAST UPDATED: 27 MAR 2000 (20000327/UP).  FILE COVERS 1960 TO DATE.

 MEDLINE has been reloaded to reflect the annual MeSH changes made by
 the National Library of Medicine for 2000. Enter HELP RLOAD for details.

 OLDMEDLINE,  data from 1960 through 1965 from the Cumulated Index
 Medicus (CIM), has been added to MEDLINE. See HELP CONTENT for details.

 Left, right, and simultaneous left and right truncation are available in the
 Basic Index.  See HELP SFIELDS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.
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=> d que l63

L1             2 SEA FILE=REGISTRY ABB=ON  (METFORMIN/CN OR "METFORMIN HYDROCHLO
                 RIDE"/CN)
L2             2 SEA FILE=REGISTRY ABB=ON  (GLYBURIDE/CN OR "GLYBURIDE,
                 POTASSIUM SALT"/CN)
L36          847 SEA FILE=MEDLINE ABB=ON  L1
L37         2630 SEA FILE=MEDLINE ABB=ON  L2
L38       132374 SEA FILE=MEDLINE ABB=ON  DIABETES MELLITUS+NT/CT
L39         1137 SEA FILE=MEDLINE ABB=ON  (L36 OR L37) AND L38
L40           65 SEA FILE=MEDLINE ABB=ON  L39 AND (DOSE? OR DOSAGE?)(3A)(LOW OR
                 REDUC?)
L41        19781 SEA FILE=MEDLINE ABB=ON  L38(L)DT/CT
L42           58 SEA FILE=MEDLINE ABB=ON  L40 AND L41
L43            3 SEA FILE=MEDLINE ABB=ON  L42 AND (RANG? OR RATIO)
L44           75 SEA FILE=MEDLINE ABB=ON  L39 AND L41 AND (RANG? OR RATIO)
L45           41 SEA FILE=MEDLINE ABB=ON  L44 AND (DOSE? OR DOSAGE?)
L46        33472 SEA FILE=MEDLINE ABB=ON  DRUG ADMINISTRATION SCHEDULE+NT/CT
L47            3 SEA FILE=MEDLINE ABB=ON  L45 AND L46
L48            4 SEA FILE=MEDLINE ABB=ON  L42 AND L46
L49            2 SEA FILE=MEDLINE ABB=ON  L44 AND (DOSE? OR DOSAGE?)(3A)(DOS?
                 OR DOSAGE?)
L50            3 SEA FILE=MEDLINE ABB=ON  L44 AND (RANG? OR RATIO)(3A)(DOSE? OR
                 DOSAGE?)
L55           44 SEA FILE=MEDLINE ABB=ON  L43 OR L45 OR L47 OR L48 OR L49 OR
                 L50
L63            8 SEA FILE=MEDLINE ABB=ON  L55 AND (LOW? OR REDUC?)(3A)(DOSE? OR
                 DOSAGE?)


=> file embase

FILE 'EMBASE' ENTERED AT 13:39:46 ON 29 MAR 2000
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 FILE COVERS 1974 TO 23 Mar 2000 (20000323/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l62

L1             2 SEA FILE=REGISTRY ABB=ON  (METFORMIN/CN OR "METFORMIN HYDROCHLO
                 RIDE"/CN)
L2             2 SEA FILE=REGISTRY ABB=ON  (GLYBURIDE/CN OR "GLYBURIDE,
                 POTASSIUM SALT"/CN)
L56         2933 SEA FILE=EMBASE ABB=ON  L1
L57         6891 SEA FILE=EMBASE ABB=ON  L2
L58       114190 SEA FILE=EMBASE ABB=ON  DIABETES MELLITUS+NT/CT
L59          809 SEA FILE=EMBASE ABB=ON  L56 AND L57 AND L58
L61          190 SEA FILE=EMBASE ABB=ON  L59 AND (CB/CT OR DRUG COMBINATION/CT)

L62           16 SEA FILE=EMBASE ABB=ON  L61 AND (LOW? OR REDUC?)(3A)(DOSE? OR
                 DOSAGE?)


=> dup rem 128 135 163 162

FILE 'HCAPLUS' ENTERED AT 13:40:03 ON 29 MAR 2000
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KATHLEEN FULLER EIC 1700 308-4290

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FILE 'MEDLINE' ENTERED AT 13:40:03 ON 29 MAR 2000

FILE 'EMBASE' ENTERED AT 13:40:03 ON 29 MAR 2000
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PROCESSING COMPLETED FOR L28
PROCESSING COMPLETED FOR L35
PROCESSING COMPLETED FOR L63
PROCESSING COMPLETED FOR L62
L64 92 DUP REM L28 L35 L63 L62 (10 DUPLICATES REMOVED)

=> d l64 all 1-92

L64 ANSWER 1 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:10630 HCAPLUS
DN 132:44986
TI **Combinations** of glitazones, biguanides, and optional sulfonylureas for treatment of **diabetes**
IN Whitcomb, Randall Wayne
PA Warner-Lambert Company, USA
SO U.S., 22 pp., Cont.-in-part of U.S. 5,859,037.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-44
ICS A61K031-425; A61K031-175; A61K031-155
NCL 514369000
CC 1-10 (Pharmacology)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6011049	A	20000104	US 1998-189132	19981109
	US 5859037	A	19990112	US 1997-970057	19971113
PRAI	US 1997-38224		19970219		
	US 1997-970057		19971113		

AB **Combinations** of a glitazone antidiabetic agent and a biguanide antidiabetic agent, and optionally a sulfonylurea antidiabetic agent, are useful for treating **diabetes** mellitus and improving glycemic control.
ST glitazone biguanide **combination diabetes** treatment; sulfonylurea glitazone biguanide **combination diabetes** treatment
IT Antidiabetic agents
(**combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)
IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)
IT **Diabetes** mellitus
(non-insulin-dependent; **combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)
IT Drug interactions
(synergistic; **combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)
IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 451-71-8, Glyhexamide **657-24-9**, Metformin 664-95-9, Tolcyclamide 968-81-0, Acetohexamide 1156-19-0, Tolazamide

3149-00-6, Phenbutamide **10238-21-8**, Glyburide 21187-98-4, Gliclazide 25046-79-1, Glisoxepid 26944-48-9, Glibornuride 29094-61-9, Glipizide 33342-05-1, Gliquidone 97322-87-7, Troglitazone 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)

IT 50-99-7, D-Glucose, biological studies 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**combinations** of glitazones, biguanides, and optional sulfonylureas for **diabetes** treatment)

L64 ANSWER 2 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:152222 HCAPLUS
DN 132:175614
TI Addition of **low-dose** rosiglitazone to sulphonylurea **therapy** improves glycemic control in Type 2 diabetic patients
AU Wolffenbuttel, B. H. R.; Gomist, R.; Squatrito, S.; Jones, N. P.; Patwardhan, R. N.
CS University Hospital Maastricht, Maastricht, 6202 AZ, Neth.
SO Diabetic Med. (2000), 17(1), 40-47
CODEN: DIMEEV; ISSN: 0742-3071
PB Blackwell Science Ltd.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Aims: This study was designed to test the efficacy and safety of **low-dose** rosiglitazone, a potent, insulin-sensitizing thiazolidinedione, in combination with sulfonylurea in Type 2 diabetic patients. Methods: For the intention-to-treat anal., 574 patients (59% male, mean age 61 yr) were available, randomized to receive 26 wk of twice-daily placebo (n = 192), rosiglitazone 1 mg (n = 199) or rosiglitazone 2 mg (n = 183) in addn. to existing sulfonylurea treatment with gliclazide (47.6% of patients), glibenclamide (41.8%) or glipizide (9.4%) (two patients were taking carbutamide or glimepiride). Change in Hb A1c (HbA1c), fasting plasma glucose (FPG), fructosamine, insulin, C-peptide, albumin, and lipids were measured, and safety was evaluated. Results: Mean baseline HbA1c was 9.2% and FPG was 11.4 mmol/l. Rosiglitazone at doses of 1 and 2 mg b.d. plus sulfonylurea produced significant decreases, compared with sulfonylurea plus placebo, in HbA1c (-0.59% and -1.03%, resp.; both $P < 0.0001$) and FPG (1.35 mmol/l and 2.44 mmol/l, resp.; both $P < 0.0001$). Both HDL-cholesterol and LDL-cholesterol increased and potentially beneficial decreases in non-esterified fatty acids and gamma glutamyl transpeptidase levels were seen in both rosiglitazone groups. The overall incidence of adverse experiences was similar in all three treatment groups, with no significant cardiac events, hypoglycemia or hepatotoxicity. Conclusions: Overall, the combination of rosiglitazone and a sulfonylurea was safe, well tolerated and effective in patients with Type 2 **diabetes**.
ST rosiglitazone sulfonylurea antidiabetic gliclazide glibenclamide NIDDM; glipizide carbutamide glimepiride antidiabetic NIDDM
IT Antidiabetic agents
(addn. of **low-dose** rosiglitazone to sulfonylurea **therapy** improves glycemic control in type 2 diabetic humans)
IT Sulfonylureas
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(addn. of **low-dose** rosiglitazone to sulfonylurea **therapy** improves glycemic control in type 2 diabetic humans)
IT 339-43-5, Carbutamide **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide 29094-61-9, Glipizide 93479-97-1, Glimepiride 122320-73-4, Rosiglitazone

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(addn. of **low-dose** rosiglitazone to sulfonylurea **therapy** improves glycemic control in type 2 diabetic humans)

IT 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(addn. of **low-dose** rosiglitazone to sulfonylurea **therapy** improves glycemic control in type 2 diabetic humans)

L64 ANSWER 3 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
AN 1999:390370 HCAPLUS
DN 131:35883
TI Novel salts of metformin and method
IN Timmins, Peter; Winter, William J.; Srivastava, Sushil K.; Bretnall, Alison; Wei, Chenkou; Powers, Gerald L.
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-155
CC 63-6 (**Pharmaceuticals**)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9929314	A1	19990617	WO 1998-US25104	19981201
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9916026	A1	19990628	AU 1999-16026	19981201
US 6031004	A	20000229	US 1999-262526	19990304
PRAI US 1997-986586	19971208			
WO 1998-US25104	19981201			

AB Novel salts of the antidiabetic agent metformin are provided which are metformin salts of dibasic acids (2:1 molar ratio), preferably metformin (2:1) fumarate and metformin (2:1) succinate, which may be employed alone or in **combination** with another antihyperglycemic agent such as glyburide, for treating **diabetes**. A method for treating **diabetes** employing the novel metformin salt by itself or in **combination** with another antidiabetic agent is also provided. A tablet contained metformin fumarate (2:1) 600, microcryst. cellulose 80, Na Croscarmellose 45, Povidone 15, and Mg stearate 8 mg.

ST antidiabetic tablet metformin dibasic acid salt

IT Antidiabetic agents
(antidiabetic compns. contg. metformin salts and antihyperglycemic agents)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antidiabetic compns. contg. metformin salts and antihyperglycemic agents)

IT Drug delivery systems
(capsules; antidiabetic compns. contg. metformin salts and antihyperglycemic agents)

IT Drug delivery systems
(tablets, chewable; antidiabetic compns. contg. metformin salts and antihyperglycemic agents)

IT Drug delivery systems

(tablets; antidiabetic compns. contg. metformin salts and antihyperglycemic agents)
IT 226880-93-9P 226880-94-0P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); **THU (Therapeutic use)** ; BIOL (Biological study); PREP (Preparation); USES (Uses)
(antidiabetic compns. contg. metformin salts and antihyperglycemic agents)
IT 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8, Insulin, biological studies **10238-21-8**, Glyburide 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 93479-97-1, Glimepiride 97322-87-7, Troglitazone 226880-95-1
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antidiabetic compns. contg. metformin salts and antihyperglycemic agents)
IT 9033-06-1, Glucosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antidiabetic compns. contg. metformin salts and antihyperglycemic agents)
IT **657-24-9**, Metformin
RL: RCT (Reactant)
(prepn. of metformin dibasic acid salts)

L64 ANSWER 4 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
AN 1999:81574 HCAPLUS
DN 130:134188
TI Treatment of **diabetes** with a thiazolidinedione, an insulin secretagogue, and a biguanide
IN Buckingham, Robin Edwin; Smith, Stephen Alistair
PA Smithkline Beecham PLC, UK
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-44; A61K031-155; A61K031-64; A61K031-44; A61K031-155
CC 1-10 (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9903477	A1	19990128	WO 1998-GB2110	19980716
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9884488	A1	19990210	AU 1998-84488	19980716

PRAI GB 1997-15295 19970718
WO 1998-GB2110 19980716
AB A method and **compn**. are disclosed for the treatment of **diabetes** mellitus and conditions assocd. with **diabetes** mellitus in a mammal. The method comprises administering an effective nontoxic and **pharmaceutically** acceptable amt. of an insulin sensitizer, an insulin secretagogue and a biguanide antihyperglycemic agent to a mammal in need thereof.
ST thiazolidinedione insulin secretagogue biguanide antidiabetic; sensitizer secretagogue insulin biguanide antidiabetic
IT Antidiabetic agents
Drug delivery systems

Tablets (drug delivery systems)
(thiazolidinedione, insulin secretagogue, and biguanide for **diabetes** treatment)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and biguanide for **diabetes** treatment)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensitizers and secretagogues; thiazolidinedione, insulin secretagogue, and biguanide for **diabetes** treatment)

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 114-86-3, Phenformin 339-43-5, Carbutamide 631-27-6, Glyclopyramide **657-24-9**, Metformin 664-95-9, Glycyclamide 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 74772-77-3, Ciglitazone 93479-97-1, Glimepiride 97322-87-7, Troglitazone 109229-58-5, Englitazone 111025-46-8, Pioglitazone 122320-73-4 135062-02-1, Repaglinide 155141-29-0
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and biguanide for **diabetes** treatment)

L64 ANSWER 5 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:566077 HCAPLUS
DN 131:194808
TI GLP-1 derivatives of GLP-1 and exendin with a protracted profile of action
IN Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf; Nielsen, Per Franklin; Madsen, Kjeld
PA Novo Nordisk A/s, Den.
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-605
ICS A61K038-26
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 34, **63**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9943708	A1	19990902	WO 1999-DK86	19990225
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9932477	A1	19990915	AU 1999-32477	19990225

PRAI DK 1998-274 19980227
US 1998-PV84357 19980505
WO 1999-DK86 19990225

AB The present invention relates to derivs. exendin and of GLP-1(7-C), wherein C is 35 or 36, which derivs. have just one lipophilic substituent which is attached to the C-terminal amino acid residue. The derivs. have a protracted action relative to GLP-1(7-37) and are useful for treating insulin-dependent and noninsulin-dependent **diabetes** mellitus.

The derivs. of the invention can be **combined** with other antidiabetics or oral hypoglycemic agents. **Pharmaceutical** formulations contg. the derivs. of the invention are also claimed.

ST GLP1 exendin lipophilic derivs prepn insulinotropic

IT Antidiabetic agents
(GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT Antiobesity agents
Drug delivery systems
(GLP-1 and exendin lipophilic derivs. with a protracted profile for treating **diabetes** mellitus and obesity)

IT **Diabetes** mellitus
(insulin-dependent; GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT **Diabetes** mellitus
(non-insulin-dependent; GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT Drug interactions
(synergistic; GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide **657-24-9**, Metformin **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide 29094-61-9, Glipizide 56180-94-0, Acarbose 74772-77-3, Ciglitazone 97322-87-7, Troglitazone 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT 133514-43-9DP, 9-39-Exendin 3 (Heloderma horridum), lipophilic derivs. 165338-05-6DP, 1-31-Exendin 4 (Heloderma suspectum), lipophilic derivs. 165338-06-7DP, lipophilic derivs. 204655-89-0DP, lipophilic derivs. 204655-90-3DP, lipophilic derivs. 204655-91-4DP, lipophilic derivs. 204656-66-6DP, lipophilic derivs. 204656-68-8DP, lipophilic derivs. 240805-46-3DP, lipophilic derivs. 240805-53-2DP, lipophilic derivs.
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(GLP-1 and exendin lipophilic derivs. with a protracted profile for treating **diabetes** mellitus and obesity)

IT 2295-31-0D, Thiazolidinedione, derivs.
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(GLP-1 and exendin lipophilic derivs. with a protracted profile for treating **diabetes** mellitus and obesity)

IT 9033-06-1, Glucosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, as oral hypoglycemic agents; GLP-1 and exendin lipophilic derivs. with a protracted action in **combinations** with other antidiabetics or oral hypoglycemic agents for treating **diabetes** mellitus)

IT 106612-94-6DP, Glucagon-like peptide I(7-37) (human), lipophilic derivs. 107444-51-9DP, (7-36)Glucagon-like peptide-1 amide (human), lipophilic derivs. 204521-68-6DP, lipophilic derivs. 204521-69-7DP, lipophilic

derivs. 204521-70-0DP, lipophilic derivs. 204521-72-2DP, lipophilic derivs. 204521-72-2P 204521-81-3DP, lipophilic derivs. 204521-82-4DP, lipophilic derivs. 204521-83-5DP, lipophilic derivs. 204521-84-6DP, lipophilic derivs. 204521-85-7DP, lipophilic derivs. 204521-86-8DP, lipophilic derivs. 204521-87-9DP, lipophilic derivs. 204521-88-0DP, lipophilic derivs. 204521-89-1DP, lipophilic derivs. 204521-90-4DP, lipophilic derivs. 204521-91-5DP, lipophilic derivs. 204521-92-6DP, lipophilic derivs. 204655-84-5DP, lipophilic derivs. 204655-85-6DP, lipophilic derivs. 204655-86-7DP, lipophilic derivs. 204655-92-5DP, lipophilic derivs. 204655-93-6DP, lipophilic derivs. 204656-04-2DP, lipophilic derivs. 204656-05-3DP, lipophilic derivs. 204656-06-4DP, lipophilic derivs. 204656-07-5DP, lipophilic derivs. 204656-12-2DP, lipophilic derivs. 204656-13-3DP, lipophilic derivs. 204656-14-4DP, lipophilic derivs. 204656-15-5DP, lipophilic derivs. 204656-22-4DP, lipophilic derivs. 204656-24-6DP, lipophilic derivs. 204656-29-1DP, lipophilic derivs. 204656-32-6DP, lipophilic derivs. 204656-37-1DP, lipophilic derivs. 204656-39-3DP, lipophilic derivs. 204656-42-8DP, lipophilic derivs. 204656-43-9DP, lipophilic derivs. 204656-44-0DP, lipophilic derivs. 204656-45-1DP, lipophilic derivs. 204656-46-2DP, lipophilic derivs. 204656-47-3DP, lipophilic derivs. 204656-48-4DP, lipophilic derivs. 204656-49-5DP, lipophilic derivs. 204656-50-8DP, lipophilic derivs. 204656-52-0DP, lipophilic derivs. 204656-53-1DP, lipophilic derivs. 204656-54-2DP, lipophilic derivs. 204656-55-3DP, lipophilic derivs. 204656-56-4DP, lipophilic derivs. 204656-57-5DP, lipophilic derivs. 204656-58-6DP, lipophilic derivs. 204656-59-7DP, lipophilic derivs. 204656-60-0DP, lipophilic derivs. 204656-62-2DP, lipophilic derivs. 204656-64-4DP, lipophilic derivs. 204656-65-5P 204656-69-9DP, lipophilic derivs. 204656-70-2DP, lipophilic derivs. 204656-71-3DP, lipophilic derivs. 204656-72-4DP, lipophilic derivs. 204656-73-5DP, lipophilic derivs. 204656-75-7DP, lipophilic derivs. 204656-76-8DP, lipophilic derivs. 204656-77-9DP, lipophilic derivs. 204656-78-0DP, lipophilic derivs. 204656-79-1DP, lipophilic derivs. 204656-80-4DP, lipophilic derivs. 204656-81-5DP, lipophilic derivs. 204656-82-6DP, lipophilic derivs. 204656-83-7DP, lipophilic derivs. 204656-85-9DP, lipophilic derivs. 204656-86-0DP, lipophilic derivs. 204656-87-1DP, lipophilic derivs. 204656-88-2DP, lipophilic derivs. 204656-89-3DP, lipophilic derivs. 204656-90-6DP, lipophilic derivs. 204656-91-7DP, lipophilic derivs. 204656-92-8DP, lipophilic derivs. 204656-93-9DP, lipophilic derivs. 204656-94-0DP, lipophilic derivs. 204656-95-1DP, lipophilic derivs. 204656-96-2DP, lipophilic derivs. 204656-97-3DP, lipophilic derivs. 213190-65-9DP, Exendin, lipophilic derivs. 240480-97-1P 240480-98-2P 241488-76-6P 241488-86-8P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis of GLP-1 and exendin lipophilic derivs. with a protracted action in treating **diabetes** mellitus)

IT 45120-30-7 204521-71-1 240133-34-0 241488-82-4 241488-98-2

RL: RCT (Reactant)

(synthesis of GLP-1 and exendin lipophilic derivs. with a protracted action in treating **diabetes** mellitus)

IT 204521-63-1P 204521-65-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(synthesis of GLP-1 and exendin lipophilic derivs. with a protracted action in treating **diabetes** mellitus)

L64 ANSWER 6 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

AN 1999-571771 [48] WPIDS

DNC C1999-166815

TI Biphasic controlled release delivery system.

DC A11 A96 B05

IN DENNIS, A B; TIMMINS, P; VYAS, K A

PA (BRIM) BRISTOL-MYERS SQUIBB CO

CYC 80
PI WO 9947128 A1 19990923 (199948)* EN 41p A61K009-24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9931828 A 19991011 (200008) A61K009-24
ADT WO 9947128 A1 WO 1999-US5233 19990310; AU 9931828 A AU 1999-31828 19990310
FDT AU 9931828 A Based on WO 9947128
PRAI US 1998-44446 19980319
IC ICM A61K009-24
AB WO 9947128 A UPAB: 19991122
NOVELTY - Biphasic controlled release delivery system has:
(a) an inner solid particulate phase in which the particles comprise a highly water soluble pharmaceutical and an extended release material;
(b) an outer solid continuous phase in which the particles in (a) are embedded, this phase also comprising an extended release material.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of preparing a biphasic controlled release delivery system, by:
(1) forming an inner solid particulate phase comprising a highly water soluble pharmaceutical and an extended release material, and
(2) mixing the individual particles forming the inner solid particulate phase with an outer solid continuous phase comprising an extended release material, in order to disperse and embed the individual particles forming the inner solid particulate phase in the outer solid continuous phase.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The formulation is preferably a biphasic heterogeneous controlled release formulation which is designed to release pharmaceutical from the particles forming the inner solid particulate phase through the outer solid continuous phase into the upper gastrointestinal tract and is particularly useful for the delivery of **metformin** hydrochloride in the treatment of **diabetes** (claimed). When containing **metformin**, the biphasic formulation can be used in the treatment of hyperglycemia including Type II and/or Type I **diabetes**.
ADVANTAGE - The new dosage form for highly water soluble medicaments provides for extended release and prolonged gastric residence which enables efficient delivery of drugs normally absorbed in the upper gastrointestinal tract. This has been achieved without the need for co-administration of the drug with other drugs (e.g. propantheline) and for low density formulation or gas penetration. Extended gastric residence is achieved by virtue of size but the formulation will degrade in vivo so as to avoid potential gastric obstruction. The initial burst of drug is controlled. Interpatient variability in pharmacokinetic parameters is minimized. Ethylcellulose N10 NF (25 g) in EtOH (100 ml) was gradually added to **metformin** hydrochloride (500 g) in a planetary mixer to give a uniform damp granulation which was dried at 55 deg. C for 1 hour and passed through an 8 mm screen to break down the agglomerates. The **metformin**-ethylcellulose granules (541 g) were blended with hydroxypropylmethylcellulose 2208 USP (351.5 g) (100000 cps grade), hydroxypropymethylcellulose 2910 USP (5 cps grade) and microcrystalline cellulose in a planetary mixer for 10 minutes. The mix was lubricated with magnesium stearate (1 w/w%) and compressed into capsules containing 500 mg **metformin** hydrochloride. When subjected to in vitro drug release testing, the amount of **metformin** released over 1,2,3,4,5,6,7 and 8 hours was 38.1, 56.3, 69.5, 79.7, 87.4, 93.1, 97.7 and 100% respectively.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A03-A04A1; A12-V01; B04-C03; B10-A17; B12-M10; B14-F09; B14-S04

L64 ANSWER 7 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-561837 [47] WPIDS
DNC C1999-163768
TI Controlled release antihyperglycemic tablet independent of food intake.
DC A11 A14 A96 B07
IN CHEN, C; CHENG, X X; CHOU, J; JAN, S
PA (ANDR-N) ANDRX PHARM INC
CYC 81
PI WO 9947125 A1 19990923 (199947)* EN 29p A61K009-20
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9931019 A 19991011 (200008) A61K009-20
ADT WO 9947125 A1 WO 1999-US6024 19990319; AU 9931019 A AU 1999-31019 19990319
FDT AU 9931019 A Based on WO 9947125
PRAI US 1998-45330 19980320
IC ICM A61K009-20
AB WO 9947125 A UPAB: 19991116
NOVELTY - Controlled release pharmaceutical tablet comprises:
(1) a core comprising antihyperglycemic drug and optionally binding agent and absorption enhancer;
(2) a semipermeable membrane coating for the core and
(3) at least one passageway in the membrane.
ACTIVITY - Antihyperglycemic.
MECHANISM OF ACTION - None given.
USE - Used in control and management of non-insulin dependent **diabetes** mellitus (NIDDM) for providing continuous and non-pulsating therapeutic levels of drug over a 12 or 24 hour period.
ADVANTAGE - The product shows a smoother release profile with time than prior art products. The bioavailability of the drug is not decreased by the presence of food. The osmotic core can also be prepared by ordinary tablet compression techniques.
Dwg.0/8
FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C02A; B04-C03B; B04-C03D; B05-A01A; B05-A01B; B10-A09B; B10-A17; B10-B01B; B10-C04E; B10-G02; B12-M10A; B14-F09

L64 ANSWER 8 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-287866 [24] WPIDS
DNC C1999-085020
TI Once-daily controlled release dosage forms for oral administration of glipizide or its salts.
DC A11 A96 B05
IN BAICHWAL, A R; BHAGWAT, D; DIEHL, D
PA (MEND-N) MENDELL CO INC EDWARD
CYC 83
PI WO 9918932 A1 19990422 (199924)* EN 49p A61K009-10
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
ZA 9809542 A 19990728 (199935)# 45p A61K000-00
AU 9910877 A 19990503 (199937) A61K009-10
ADT WO 9918932 A1 WO 1998-US21752 19981015; ZA 9809542 A ZA 1998-9542 19981020; AU 9910877 A AU 1999-10877 19981015
FDT AU 9910877 A Based on WO 9918932
PRAI US 1997-950732 19971015; ZA 1998-9542 19981020

IC ICM A61K000-00; A61K009-10
ICS A61K009-16; A61K009-32; A61K009-34; A61K009-52; A61K047-36
AB WO 9918932 A UPAB: 19990624
NOVELTY - A novel solid matrixed controlled released oral dosage comprising sulfonylurea is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(1) controlled release dosage forms for oral administration which comprise:
(a) a therapeutically effective amount of glipizide or its pharmaceutically acceptable salts; and
(b) a controlled-release matrix comprising a gelling agent, an ionizable gel strength enhancing agent and an inert diluent, and
(2) a method of manufacturing the controlled release dosage form of (1).
The **ratio** of gelling agent to inert diluent is 1:8-8:1. The gelling agent comprises xanthan gum and locust bean gum in a **ratio** of 3:1-1:3.
The ionizable gel strength enhancing agent increases the strength of the controlled-release matrix, and the glipizide is suspended or dissolved in a pharmaceutically acceptable wetting agent prior to incorporation with the remaining ingredients of the controlled-release matrix.
ACTIVITY - Anti-**diabetic**.
USE - The controlled release composition is useful in the treatment of type II **diabetes**. Used for once-daily dosing of glipizide (claimed) and other sulfonylureas including tolbutamide, chlorpropamide, tolazamide, acetohexamide, **glyburide**, glibornuride, glisoxepide, and gliclazide.
A single-dose, randomized, crossover biostudy in the fasted condition compared the bioavailability of test composition tablets with a commercially available product with the same dosage strength, but different release mechanism prescribed as a once-daily adjunct to a controlled diet for the control of hyperglycemia and associated symptomatology in patients with non-insulin dependent **diabetes** mellitus. The study was performed in 12 normal, healthy, male volunteers. In test fasted and reference fasted patients, respectively, Tmax values (hours) were 8 and 6 hours, respectively, AUCs (nghv/ml) were 4716 and 5107, respectively and Cmax values (mg/ml) were 268 and 284, respectively.
ADVANTAGE - Suitable for once-daily dosing of glipizide. Avoids the need for construction of complex devices for oral administration, simplifies treatment and improve patients compliance while enhancing the bioavailability of the anti-**diabetic** drug and prolonging the release of the drug. Alkalizing or acidifying medium affords substantially complete bioavailability from the sustained-release matrix. Method is more economical for the stable and convenient treatment of **diabetes** responsive to glipizide.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A03-A00A; A12-V01; B04-C02A2; B04-C02D; B12-M10A; B14-S04

L64 ANSWER 9 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-131848 [11] WPIDS
DNC C1999-038486
TI **Diabetes** treatment - uses combination of non-toxic insulin sensitiser and sub-maximal amount of insulin secretagogue for improved glycaemic control especially in type II **diabetes**.
DC B05
IN BUCKINGHAM, R E; SMITH, S A
PA (SMIK) SMITHKLINE BEECHAM PLC
CYC 82
PI WO 9903476 A1 19990128 (199911)* EN 17p A61K031-64
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE

GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW
AU 9884487 A 19990210 (199925) A61K031-64
ADT WO 9903476 A1 WO 1998-GB2109 19980716; AU 9884487 A AU 1998-84487 19980716
FDT AU 9884487 A Based on WO 9903476
PRAI GB 1997-15306 19970718
IC ICM A61K031-64
ICS A61K031-44
ICI A61K031-64, A61K031:44
AB WO 9903476 A UPAB: 19990316
Treating **diabetes** mellitus and conditions associated with it in mammals involves administration of an effective amount of a non-toxic insulin sensitiser (I) and a sub-maximal amount of an insulin secretagogue (II).
USE - The co-administration of the two compounds provides an effective treatment for glycaemic control, the **reduced dosage** of the secretagogue **reducing** the likelihood of hypoglycaemic episodes. The non-toxic composition is effective for the treatment of **diabetes** mellitus, especially type II, and conditions associated with it.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B06-A01; B06-D03; B06-D04; B07-H; B10-A08; B14-S04

L64 ANSWER 10 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-481338 [41] WPIDS
DNC C1999-141771
TI Synergistic hypoglycemic mixture of **metformin** and fenofibrate or bezafibrate, used for treating non-insulin dependent **diabetes**.
DC B05
IN BONHOMME, Y; BRIET, P
PA (LIPH) LIPHA LYONNAISE IND PHARM; (MERE) MERCK PATENT GMBH
CYC 85
PI FR 2774591 A1 19990813 (199941)* 13p A61K031-155
WO 9940904 A2 19990819 (199941) EN A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD
GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
UA UG US UZ VN YU ZW
ZA 9901077 A 19991027 (199951) 14p A61K000-00
AU 9929233 A 19990830 (200003) A61K031-00
ADT FR 2774591 A1 FR 1998-1709 19980212; WO 9940904 A2 WO 1999-EP614 19990130; ZA 9901077 A ZA 1999-1077 19990210; AU 9929233 A AU 1999-29233 19990130
FDT AU 9929233 A Based on WO 9940904
PRAI FR 1998-1709 19980212
IC ICM A61K000-00; A61K031-00; A61K031-155
ICI A61K031-155, A61K031:215; A61K031-155, A61K031:19
AB FR 2774591 A UPAB: 19991011
NOVELTY - A pharmaceutical composition contains **metformin** (I) (or its salt) and fenofibrate (IIa) or bezafibrate (IIb), together with excipients.
ACTIVITY - Hypoglycemic.
Non-insulin-dependent **diabetes** was induced in rats by injection of streptozotocin (SZT) (45 mg/kg, i.p.), followed by oral administration of (I) and/or (IIa) or (IIb). The blood sugar levels (in g/l) were as follows: untreated controls 1.06; SZT alone 2.68; SZT + 50 mg/kg (I) 1.74; SZT + 50 mg/kg (IIa) 1.93; SZT + 50 mg/kg (IIb) 2.2; SZT + 50 mg/kg (I) + 50 mg/kg (IIa) 1.44; SZT + 50 mg/kg (I) + 50 mg/kg (IIb) 1.43.
MECHANISM OF ACTION - None given.

USE - For treatment of non-insulin dependent **diabetic** hyperglycemia, especially in non-dyslipidemic patients (claimed).

ADVANTAGE - (I) (a known hypoglycemic agent) and (IIa/b) (known hypolipemic agents) have a synergistic hypoglycemic effect.

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B10-A17; B10-C04B; B10-F02; B14-F06; B14-F09; B14-S04; B14-S09

L64 ANSWER 11 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 2000035254 EMBASE
TI Poorly controlled elderly Type 2 diabetic patients: The effects of increasing sulphonylurea dosages or adding metformin.
AU Gregorio F.; Ambrosi F.; Manfrini S.; Velussi M.; Carle F.; Testa R.; Merante D.; Filipponi P.
CS Dr. F. Gregorio, 'E. Profili' General Hospital, 60044 Fabriano (AN), Italy. gregfra@tin.it
SO Diabetic Medicine, (1999) 16/12 (1016-1024).
Refs: 31
ISSN: 0742-3071 CODEN: DIMEEV
CY United Kingdom
DT Journal; Article
FS 003 Endocrinology
020 Gerontology and Geriatrics
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Aims: To assess the effects and safety of increasing sulphonylurea dosages or adding metformin in poorly controlled elderly Type 2 diabetic patients. Methods: A 18-month multicentre clinical study was performed on sulphonylurea-treated diabetic patients over 70 years of age with well-preserved renal function, steady fasting blood glucose .gtoreq. 200 mg/dl and HbA(1c) .gtoreq. 9%. Patients were randomly assigned to sulphonylurea increased up to its maximum dosage (1st group) or to addition of metformin (2nd group). Glycaemic control, lipid pattern, haemostatic status and safety were monitored during run-in, at baseline and at scheduled intervals for 18 months. Results refer to 85 patients in the 1st group and 89 patients in the 2nd with complete data. Results: Similar improvements in glycaemic levels were observed with both treatments within the first month and a similar decrease in HbA(1c) within the third month. No further changes occurred in glycaemic control. In the 1st group, fasting glucose (mmol/l, mean .+-. SE) decreased from 14.21 .+-. 0.49 to 9.88 .+-. 0.21, average day-long glucose from 14.87 .+-. 0.27 to 10.69 .+-. 0.19 and HbA(1c) (%) from 10.32 .+-. 0.13 to 8.66 .+-. 0.13. In the 2nd treatment group fasting glucose decreased from 14.59 .+-. 0.61 to 9.05 .+-. 37.28, average day-long glucose from 15.09 .+-. 0.29 to 10.32 .+-. 0.21 and HbA(1c) from 10.33 .+-. 0.13 to 8.77 .+-. 0.12 (for all $P < 0.0005$). In this 2nd group, a decrease in LDL-cholesterol ($P < 0.05$) and an increase in HDL-cholesterol levels ($P < 0.02$) were also observed. In the 1st group, anthrombin III activity increased significantly ($P < 0.01$). In the 2nd group, significant reductions in markers of platelet function (FP4 and .beta.TG, $P < 0.01$), thrombin generation (FPA, F1 + 2 and D-D, $P < 0.01$), and fibrinolysis inhibition (PAI-1 activity, PAI-1 antigen, $P < 0.001$) were observed. Increases in some fibrinolytic activation markers (t-PA activity, and AT-III activity, $P < 0.01$) occurred. Fasting lactate concentrations were unchanged in the metformin-treated group. No serious adverse effects were observed in either group. Conclusions: These results suggest that either high sulphonylurea dosages or a therapy combining **lower** sulphonylurea **dosages** with metformin are effective and safe in an aged but healthy population. Metformin provides additional benefits counteracting several cardiovascular risk factors but must be administered with caution, bearing in mind the general contra-indications for the drug but not age alone.

CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
dose calculation
combination chemotherapy
drug efficacy
glucose homeostasis
cholesterol blood level
lactate blood level
hemostasis
nausea: SI, side effect
abdominal discomfort: SI, side effect
hypoglycemia: SI, side effect
human
male
female
major clinical study
clinical trial
randomized controlled trial
multicenter study
controlled study
aged
article
Drug Descriptors:
*oral antidiabetic agent: AE, adverse drug reaction
*oral antidiabetic agent: CT, clinical trial
***oral antidiabetic agent: CB, drug combination**
*oral antidiabetic agent: DO, drug dose
*oral antidiabetic agent: DT, drug therapy
*sulfonylurea derivative: AE, adverse drug reaction
*sulfonylurea derivative: CT, clinical trial
***sulfonylurea derivative: CB, drug combination**
*sulfonylurea derivative: DO, drug dose
*sulfonylurea derivative: DT, drug therapy
*metformin: AE, adverse drug reaction
*metformin: CT, clinical trial
***metformin: CB, drug combination**
*metformin: DT, drug therapy
glibenclamide: AE, adverse drug reaction
glibenclamide: CT, clinical trial
glibenclamide: CB, drug combination
glibenclamide: DO, drug dose
glibenclamide: DT, drug therapy
gliclazide: AE, adverse drug reaction
gliclazide: CT, clinical trial
gliclazide: CB, drug combination
gliclazide: DO, drug dose
gliclazide: DT, drug therapy
lactic acid: EC, endogenous compound
high density lipoprotein cholesterol: EC, endogenous compound
low density lipoprotein cholesterol: EC, endogenous compound
hemoglobin A1c: EC, endogenous compound
thrombocyte factor 4: EC, endogenous compound
thrombin: EC, endogenous compound
beta thromboglobulin: EC, endogenous compound
antithrombin III: EC, endogenous compound
plasminogen activator inhibitor 1: EC, endogenous compound
RN (metformin) **1115-70-4, 657-24-9**; (glibenclamide) **10238-21-8**; (gliclazide) 21187-98-4; (lactic acid) 113-21-3, 50-21-5; (hemoglobin A1c) 62572-11-6; (thrombocyte factor 4) 37270-94-3, 69670-74-2; (thrombin) 9002-04-4; (beta thromboglobulin) 66795-42-4; (antithrombin III) 90170-80-2; (plasminogen activator inhibitor 1) 140208-23-7

L64 ANSWER 12 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1999:741086 HCAPLUS
DN 131:318091
TI The lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulphonylureas in patients with type 2 **diabetes** mellitus
AU Lindstrom, T.; Nystrom, F. H.; Olsson, A. G.; Ottosson, A.-M.; Arnqvist, H. J.
CS Faculty of Health Sciences, Linkoping University, Linkoping, S-581 85, Swed.
SO Diabetic Med. (1999), 16(10), 820-826
CODEN: DIMEEV; ISSN: 0742-3071
PB Blackwell Science Ltd.
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB Aims: To study whether changes in endogenous insulin secretion at the same glycemic control affect the plasma concns. of lipoproteins in patients with Type 2 **diabetes** mellitus. Methods: Fifteen patients, age 59.+-.2 yr (mean .+-. SEM), body wt. 86.3.+-.3.0 kg, body mass index 29.6.+-.0.9 kg/m2 were treated with sulfonylurea and insulin in combination or with insulin alone in a randomized, double-blind, crossover study. All patients were treated with a multiple daily injection regimen with the addn. of glibenclamide 10.5 mg daily or placebo tablets. Results: During combination **therapy**, the **dose** of insulin was 25% less ($P < 0.002$) and there was a 29% increase in plasma C-peptide concn. ($P = 0.01$). Plasma levels of free insulin were not changed. Plasma levels of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein (IGFBP)-1 were lowered. There were no differences in the 24-h blood glucose profiles or HbA1c (6.0.+-.0.2 vs. 6.3.+-.0.2%; $P = 0.16$). Body wt. was similar. There was a significant decrease in plasma LDL cholesterol (3.04.+-.0.24 vs. 3.41.+-.0.21 mmol/l; $P = 0.04$), apolipoprotein A1 and of lipoprotein(a) but an increase in VLDL-triglycerides (1.36.+-.0.31 vs. 0.96.+-.0.16 mmol/l; $P = 0.02$) during combination **therapy**. The **ratio** between LDL cholesterol and apolipoprotein B concns. was significantly lower during combination **therapy** ($P < 0.01$). Conclusions: Combination **therapy** with insulin and sulfonylureas increases portal insulin supply and thereby alters liver lipoprotein metab. when compared with insulin **therapy** alone.
ST insulin sulfonylurea glibenclamide lipoprotein NIDDM antidiabetic
IT Apolipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(A-I; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)
IT Apolipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(B; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)
IT Insulin-like growth factor-binding proteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(IGF-BP-1; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)
IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Lp(a); lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)
IT Globulins, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(SHBG (sex hormone-binding globulin); lipoprotein profile differs during insulin treatment alone and combination **therapy** with

insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT Glycerides, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(blood; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(high-d.; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT Antidiabetic agents
(lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(low-d.; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT **Diabetes** mellitus
(non-insulin-dependent; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(very-low-d.; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(blood; lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

IT 59112-80-0, C-Peptide 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(lipoprotein profile differs during insulin treatment alone and combination **therapy** with insulin and sulfonylureas in humans with type 2 **diabetes** mellitus)

L64 ANSWER 13 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:517915 HCAPLUS
DN 131:165178
TI Higher incidence of severe hypoglycaemia leading to hospital admission in type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas
AU Stahl, M.; Berger, W.
CS Division of Endocrinology, Diabetology and Clinical Nutrition University Hospital of Basle, Basel, CH - 4031, Switz.
SO Diabetic Med. (1999), 16(7), 586-590

CODEN: DIMEEV; ISSN: 0742-3071
PB Blackwell Science
DT Journal
LA English
CC 1-10 (Pharmacology)
AB A comparison of the frequency of severe hypoglycemia leading to hospital admission in people with Type 2 **diabetes** mellitus (DM) treated with long vs. short-acting sulfonylureas. A community based study over a 12-yr period in the population of the city of Basle, Switzerland. The no. of diabetic patients treated with oral hypoglycemic agents was established on the basis of tablet consumption and a defined daily **dose**, e.g. 7.5 mg for glibenclamide, and 50 mg for glibornuride. Twenty-eight Type 2 diabetic patients were admitted for severe hypoglycemia, with a median age of 73 yr. There were no deaths. Sixteen of these admissions were patients treated with long-acting sulfonylureas and 12 were patients treated with short-acting forms. Only 23.5% of the population with Type 2 DM in Basle were treated with long-acting sulfonylureas. With 30 345 person-years of observation, the incidence of severe hypoglycemia was 2.24 per 1000 person-years for long-acting sulfonylureas vs. 0.75 per 1000 person-year for short-acting forms, odds **ratio** 3.01 (95% confidence interval 1.35-6.77). Decreased food intake (nine patients) was a major contributing factor. Severe hypoglycemia leading to hospital admission is more common in elderly Type 2 diabetic patients treated with long-acting compared to short-acting sulfonylureas. Such long-acting sulfonylureas should be avoided.
ST glibenclamide glibornuride type two **diabetes** hypoglycemia
IT Antidiabetic agents
Hypoglycemia
(effect of long-acting vs. short-acting sulfonylureas on severe hypoglycemia leading to hospital admission in type 2 diabetic patients)
IT **Diabetes** mellitus
(non-insulin-dependent; effect of long-acting vs. short-acting sulfonylureas on severe hypoglycemia leading to hospital admission in type 2 diabetic patients)
IT **10238-21-8**, Glibenclamide 26944-48-9, Glibornuride
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of long-acting vs. short-acting sulfonylureas on severe hypoglycemia leading to hospital admission in type 2 diabetic patients)

L64 ANSWER 14 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:256379 HCAPLUS
DN 130:291392
TI Metformin-induced resumption of normal menses in 39 of 43 (91 %) previously amenorrheic women with the polycystic ovary syndrome
AU Glueck, C. J.; Wang, Ping; Fontaine, Robert; Tracy, Trent; Sieve-Smith, Luann
CS The Cholesterol Center, Jewish Hospital, Cincinnati, OH, USA
SO Metab., Clin. Exp. (1999), 48(4), 511-519
CODEN: METAAJ; ISSN: 0026-0495
PB W. B. Saunders Co.
DT Journal
LA English
CC 1-10 (Pharmacology)
Section cross-reference(s): 15
AB In 43 amenorrheic women with polycystic ovary syndrome (PCOS), 31 (74%) with fasting hyperinsulinemia (.gtoreq. 20 .mu.U/mL), our aim was to det. whether Metformin (Bristol-Myers Squibb, Princeton, NJ), which reduces hyperinsulinemia, would reverse the endocrinopathy of PCOS, allowing resumption of regular normal menses. A second aim was to assess the effects of wt. loss vs. other Metformin-induced effects on ovarian function, and to det. if there were different responses to Metformin between those who lost wt. and those who did not. A third aim was to assess assocns. between PCOS, 4G/5G polymorphism in the promoter sequence

of the plasminogen activator inhibitor-1 gene (PAI-1 gene), and PAI activity (PAI-Fx). Of the 43 women, 40 (93%) had normal fasting blood glucose and 37 had normal Hb A1C (HgA1C); only three (7%) had type 2 **diabetes** mellitus. Metformin (**1.5** to 2.25 g/d) was given for 6.**1** .+-. **5**.1 mo (**range**, **1.5** to 24), to 16 patients for less than 3 mo, to 12 for 3 to 6 mo, and to 15 for at least 6 mo. On Metformin, 39 of 43 patients (91%) resumed normal menses. The percentage of women resuming normal menses did not differ among treatment duration groups (P < .1) or among **dose** groups (P > .1). The body mass index (BMI) decreased from 36.4 .+-. 7 kg/m2 at study entry to 35.1 .+-. 6.7 on Metformin (P = .0008). Of 43 patients, 28 (67%) lost wt. (1 to 69 lb), with nine (21%) losing at least 12 lb. On Metformin, the median fasting serum insulin decreased from 26 .mu.U/mL to 22 (P = .019), testosterone decreased from 61 ng/dL to 47 (P = .003), and estradiol increased from 41 pg/mL to 71 (P = .0001). Metformin-induced improvements in ovarian function were independent of wt. loss (testosterone decrease, P < .002; estradiol increase, P < .0004). The change in response variables on Metformin did not differ (P > .05) between those who lost wt. and those who did not, excepting Lp(a), which increased 4 mg/dL in those who lost wt. and decreased 9 mg/dL in those who did not (P = .003). The change in response variables on Metformin did not differ among the five quintiles of wt. loss, excepting fasting glucose (P < .05), which increased 6 mg/dL in those who lost the least wt. on Metformin vs. those in the 60th to 80th percentile for wt. loss, in whom glucose decreased 33 mg/dL. Although the pretreatment fasting serum insulin was not significantly correlated with testosterone (r = .24, P = .13) or androstenedione (r = .27, P = .09), on Metformin, the change in insulin correlated pos. with the change in testosterone (r = .35, P = .047) and with the change in androstenedione (r = .48, P = .01). Patients were more likely than normal controls (83% v 64%, P = .016) to be heterozygous or homozygous for 4G polymorphism of the PAI-1 gene and were also more likely to have high PAI-Fx (.gtoreq.22 U/mL, 28% v 3%, .chi.2 = 10.1, P = .001). Metformin reduces the endocrinopathy of PCOS, allowing resumption of normal menses in most (91%) previously amenorrheic women with PCOS.

ST metformin polycystic ovary syndrome menses

IT Body fluid
(menses; metformin-induced resumption of normal menses in previously amenorrheic women with the polycystic ovary syndrome in relation to)

IT Polycystic ovary syndrome
(metformin-induced resumption of normal menses in previously amenorrheic women with the polycystic ovary syndrome in relation to)

IT Polymorphism (genetic)
(of plasminogen activator inhibitor-1 gene, metformin-induced resumption of menses in amenorrheic women in relation to)

IT Genes
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(polymorphism of plasminogen activator inhibitor-1 gene in metformin-induced resumption of menses in amenorrheic women in relation to)

IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin-induced resumption of normal menses in previously amenorrheic women with the polycystic ovary syndrome in relation to)

IT 140208-23-7, PAI-1
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(metformin-induced resumption of normal menses in previously amenorrheic women with the polycystic ovary syndrome in relation to)

L64 ANSWER 15 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1999:424448 HCAPLUS
DN 131:96678
TI A risk-benefit assessment of metformin in type 2 **diabetes** mellitus
AU Howlett, Harry C. S.; Bailey, Clifford J.
CS Clinical Research, West Drayton, UK
SO Drug Saf. (1999), 20(6), 489-503
CODEN: DRSAEA; ISSN: 0114-5916
PB Adis International Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 183 refs. Metformin has been used for over 40 yr as an effective glucose-lowering agent in type 2 (noninsulin-dependent) **diabetes** mellitus. Typically it reduces basal and postprandial hyperglycemia by about 25% in more than 90% of patients when either given alone or coadministered with other **therapies** including insulin during a program of managed care. Metformin counters insulin resistance and offers benefits against many features of the insulin resistance syndrome (Syndrome X) by preventing bodyweight gain, reducing hyperinsulinemia and improving the lipid profile. In contrast to sulfonylureas, metformin does not increase insulin secretion or cause serious hypoglycemia. Treatment of type 2 **diabetes** mellitus with metformin from diagnosis also offers greater protection against the chronic vascular complications of type 2 **diabetes** mellitus. The most serious complication assocd. with metformin is lactic acidosis which has an incidence of about 0.03 cases per 1000 patients years of treatment and a mortality risk of about 0.015 per 1000 patient-years. Most cases occur in patients who are wrongly prescribed the drug, particularly patients with impaired renal function (e.g. serum creatinine level >130 .mu.mol/L or >**1.5** g/L). Other major contraindications include congestive heart failure, hypoxic states and advanced liver disease. Serious adverse events with metformin are predictable rather than spontaneous and are potentially preventable if the prescribing guidelines are respected. Gastrointestinal adverse effects, notably diarrhea, occur in less than 20% of patients and remit when the **dosage** is **reduced**. The life-threatening risks assocd. with metformin are rare and could mostly be avoided by strict adherence to the prescribing guidelines. Given the 4 decades of clin. experience with metformin, its antihyperglycemic efficacy and benefits against Syndrome X, metformin offers a very favorable risk-benefit assessment when compared with the chronic morbidity and premature mortality among patients with type 2 **diabetes** mellitus.
ST review metformin antidiabetic **diabetes** mellitus NIDDM
IT Antidiabetic agents
(metformin in treatment of type 2 **diabetes** mellitus in humans)
IT **Diabetes** mellitus
(non-insulin-dependent; metformin in treatment of type 2 **diabetes** mellitus in humans)
IT **657-24-9**, Metformin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin in treatment of type 2 **diabetes** mellitus in humans)

L64 ANSWER 16 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:11065 HCAPLUS
DN 132:161072
TI Vanadyl-biguanide complexes as potential synergistic insulin mimics
AU Woo, Lenny C. Y.; Yuen, Violet G.; Thompson, Katherine H.; McNeill, John H.; Orvig, Chris
CS Department of Chemistry, University of British Columbia, Vancouver, BC,

V6T 1Z1, Can.
SO J. Inorg. Biochem. (1999), 76(3-4), 251-257
CODEN: JIBIDJ; ISSN: 0162-0134
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Vanadium has well-documented blood-glucose-lowering properties both in vitro and in vivo. The design of new oxovanadium(IV) coordination compds., intended for use as insulin-enhancing agents in the treatment of **diabetes** mellitus, can potentially benefit from a synergistic approach, in which the whole complex has more than an additive effect from its component parts. Biguanides, most importantly metformin, are oral hypoglycemic agents used today to treat type 2 **diabetes** mellitus. In this study, biguanide, metformin, and phenformin, all biguanides, were coordinated to oxovanadium(IV) to form potential insulin-enhancing compds. Highly colored, air-stable, bis(biguanidato) oxovanadium(IV), [VO(big)2], bis(N',N'-dimethylbiguanidato) oxovanadium(IV), [VO(metf)2], and bis(.beta.-phenethyl-biguanidato) oxovanadium(IV), [VO(phenf)2], were prepd. Solvation with dimethylsulfoxide occurred with VO(metf)2 to form a six-coordinate complex. Precursor ligands and oxovanadium(IV) coordination complexes were characterized by IR spectroscopy, mass spectrometry, elemental analyses, magnetic susceptibility, and, where appropriate, 1H NMR spectroscopy. Biol. testing with VO(metf)2, a representative compd., for insulin-enhancing potential included acute (72 h) administration, both by i.p. injection and by oral gavage (p.o.) in streptozotocin (STZ) -diabetic rats. VO(metf)2 administration resulted in significant blood-glucose **lowering** at **doses** of 0.12 mmol kg-1 i.p. and 0.60 mmol kg-1 p.o. (previously established as ED50 doses for organically chelated oxovanadium(IV) complexes); however, no pos. associative effects due to the presence of biguanide in the complex were apparent.
ST prepn vanadyl biguanide complex synergism hypoglycemic; insulin mimic vanadyl biguanide complex **diabetes**
IT Antidiabetic agents
(prepn. and hypoglycemic effect of potential synergistic insulin mimicking vanadyl-biguanide complexes in rat diabetic model)
IT 7440-62-2, Vanadium, reactions
RL: RCT (Reactant)
(complexes with biguanides; prepn. and hypoglycemic effect of potential synergistic insulin mimicking vanadyl-biguanide complexes in rat diabetic model)
IT 52139-14-7P 258524-63-9P 258524-68-4P 258524-73-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and hypoglycemic effect of potential synergistic insulin mimicking vanadyl-biguanide complexes in rat diabetic model)
IT 156-28-5, .beta.-Phenethylamine hydrochloride 461-58-5, Dicyandiamide **657-24-9**, Metformin
RL: RCT (Reactant)
(prepn. and hypoglycemic effect of potential synergistic insulin mimicking vanadyl-biguanide complexes in rat diabetic model)
IT 114-86-3P, Phenformin 2583-53-1P, Biguanide sulfate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hypoglycemic effect of potential synergistic insulin mimicking vanadyl-biguanide complexes in rat diabetic model)

L64 ANSWER 17 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:775210 HCAPLUS
DN 131:346352
TI Effects of antihyperglycemic **therapies** on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 **diabetes**

AU Hermann, L. S.; Ranstam, J.; Vaaler, S.; Melander, A.
CS The Swedish Network for Pharmacoepidemiology, Malmo, Swed.
SO Diabetes, Obes. Metab. (1999), 1(4), 227-232
CODEN: DOMEF6; ISSN: 1462-8902
PB Blackwell Science Ltd.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Aim: To assess the effect of oral antihyperglycemic **therapy** on fasting proinsulin and the relation between proinsulin levels and cardiovascular risk factors in type 2 **diabetes**. Methods: One hundred and sixty-five patients with type 2 **diabetes**, fasting blood glucose concn. (FBG) .gtoreq. 6.7 mmol/l, were recruited from five **diabetes** outpatient clinics in primary health care. Diet and antihyperglycemic medication, aiming at FBG <6.7 mmol/l, was maintained for 6 mo after completed dose titrn. in a randomized, double-blind, double-dummy trial with metformin (M), glibenclamide (G) and primary **combination** of both drugs (MG). The study compared M, G and MG in **low dose** (MGL) and also different high-dose regimens, i.e. G added to M (M/G), M added to G (G/M) and primary **combination** (MGH). Outcome measures were fasting proinsulin, glycemia, body mass index, blood pressure, lipids, insulin and C-peptide. Results: Lower proinsulin levels were found when **therapy** was initiated with metformin (M vs. G, p = 0.013 and M/G vs. G/M, p = 0.033). M and G were equally effective on glucose levels. In the group as a whole FBG decreased from (mean .+-. s.d.) 10.2.+-.2.7 to 7.0.+-.1.2 mmol/l with no change in proinsulin. Proinsulin was assocd. with cardiovascular risk factors, linking high proinsulin to an atherogenic risk marker profile. Mean proinsulin change from baseline was inconsistently assocd. with markers of insulin resistance. Meal-stimulated glucose (net AUC) decreased after treatment only in those with low baseline proinsulin levels. Conclusion: It may be advantageous to initiate oral antihyperglycemic **therapy** with metformin rather than with sulfonylurea. High proinsulin levels are assocd. with an atherogenic-risk marker profile and an impaired **therapeutic** postprandial glucose response after treatment in patients with type 2 **diabetes**. Proinsulin change after **therapy** is inconsistently assocd. with markers of insulin resistance and unrelated to fasting blood glucose redn.
ST antihyperglycemic metformin glibenclamide proinsulin atherogenesis NIDDM
IT Antidiabetic agents
Atherosclerosis
(effects of antihyperglycemics, metformin and glibenclamide on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 **diabetes** in humans)
IT **Diabetes** mellitus
(non-insulin-dependent; effects of antihyperglycemics, metformin and glibenclamide on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 **diabetes** in humans)
IT **657-24-9**, Metformin **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effects of antihyperglycemics, metformin and glibenclamide on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 **diabetes** in humans)
IT 9035-68-1, Proinsulin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effects of antihyperglycemics, metformin and glibenclamide on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 **diabetes** in humans)

L64 ANSWER 18 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:19014 HCAPLUS
DN 130:204954
TI Metformin reduces systemic methylglyoxal levels in type 2 **diabetes**

AU Beisswenger, Paul J.; Howell, Scott K.; Touchette, Allison D.; Lal, Sundeep; Szwergold, Benjamin S.
CS Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, Dartmouth-Hitchcock Medical Center and Dartmouth Medical School, Lebanon, NH, 03756, USA
SO Diabetes (1999), 48(1), 198-202
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Methylglyoxal (MG) is a reactive .alpha.-dicarbonyl that is thought to contribute to diabetic complications either as a direct toxin or as a precursor for advanced glycation end products. It is produced primarily from triose phosphates and is detoxified to D-lactate (DL) by the glyoxalase pathway. Because guanidino compds. can block dicarbonyl groups, the authors have investigated the effects of the diamino biguanide compd. metformin and of hyperglycemia on MG and its detoxification products in type 2 **diabetes**. MG and DL were measured by HPLC in plasma from 57 subjects with type 2 **diabetes**. Of these subjects, 27 were treated with diet, sulfonylureas, or insulin (nonmetformin), and 30 were treated with metformin; 28 normal control subjects were also studied. Glycemic control was detd. by HbA1c. MG was significantly elevated in diabetic subjects vs. the normal control subjects (189.3 vs. 123.0 nM). MG levels were significantly **reduced** by high-**dosage** (1500-2500 mg/day) metformin (158.4 nM) compared with non-metformin (189.3 nM) or **low-dosage** (.ltoreq.1000 mg/day) metformin (210.98 nM), even though the groups had similar glycemic control. Conversely, DL levels were significantly elevated in both the **low-** and high-**dosage** metformin groups relative to the nonmetformin group (13.8 and 13.4 vs. 10.4 .mu.M, and 0.06, resp.). MG correlated with rising HbA1c levels (R = 0.4, slope = 13.2) in the non-metformin subjects but showed no increase with worsening glycemic control in the high-**dosage** metformin group (R = 0.0004, slope = 0.02). In conclusion, MG is elevated in **diabetes** and relates to glycemic control. Metformin **reduces** MG in a **dose**-dependent fashion and minimizes the effect of worsening glycemic control on MG levels. To the extent that elevated MG levels lead to their development, metformin treatment may protect against diabetic complications by mechanisms independent of its antihyperglycemic effect.
ST metformin antidiabetic methylglyoxal noninsulin dependent **diabetes**
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(metformin reduces systemic methylglyoxal levels and increases lactate levels in humans with type 2 **diabetes**)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metformin reduces systemic methylglyoxal levels and increases lactate levels in humans with type 2 **diabetes**)
IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin reduces systemic methylglyoxal levels and increases lactate levels in humans with type 2 **diabetes**)
IT 50-99-7, D-Glucose, biological studies 78-98-8, Methylglyoxal 10326-41-7, D-Lactic acid, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metformin reduces systemic methylglyoxal levels and increases lactate levels in humans with type 2 **diabetes**)

L64 ANSWER 19 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:435325 HCAPLUS
DN 131:237799

TI The effects of LBP-D, hypoglycemic agents, alone or in **combination**, on blood glucose and immune functions in alloxan-induced **diabetes** mice
AU Wang, Ling; Dong, Jian; Jiang, Lu-Zhi; Zhang, Cai-Jun; Hu, Shi-Xiu; Xie, Pu-Ling; Li, Wei-Bo; Deng, Xue-Duan
CS Department of Microbiology and Immunology, Kunming Medical College, Kunming, 650031, Peop. Rep. China
SO Yunnan Daxue Xuebao, Ziran Kexueban (1999), 21(3), 186-188, 191
CODEN: YDXKES; ISSN: 0258-7971
PB Yunnan Daxue Xuebao Bianjibu
DT Journal
LA Chinese
CC 1-10 (Pharmacology)
AB An expt. diabetic model was induced by vein injection of alloxan monohydrate (100 mg/kg). We obsd. the effects of LBP-D (Lycium barbarum polysaccharide-D), and hypoglycemic agents alone or in **combination**, on blood glucose and immune functions in alloxan-induced **diabetes** mice. In the present study, the drugs were administered at 72 h after the injection of alloxan for ten days in succession. The blood glucose level in NS mice and alloxan-induced **diabetes** mice were significantly reduced by the drug, and the **combination** of LBP-D and hypoglycemic agents (glibenclamide and metformin) were able to markedly decrease blood glucose level. In addn., LBP-D changed hemolysin level and modulated the functions of lymphocyte subpopulations. It showed immune function-recovering effect in the alloxan-induced diabetic mice. These results indicated that LBP-D may have a cytoprotection effect on .beta.-cells of pancreatic islets in mice and an immune modulation therapeutic effect on **diabetes**.
ST Lycium barbarum polysaccharide hypoglycemic **diabetes** immunity
IT Polysaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D; LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT Antidiabetic agents
Cytoprotective agents
Drug interactions
Immunity
Lycium barbarum
Lymphocyte
(LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT Hemolysins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT Pancreatic islet of Langerhans
(.beta.-cell; LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT **657-24-9**, Metformin **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)
IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(blood; LBP-D alone or in **combination** with hypoglycemic agents: effect on blood glucose and immunity in **diabetes**)

L64 ANSWER 20 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1999:195262 HCAPLUS
DN 131:125252
TI Long-term **therapeutic** effectiveness of repaglinide compared with glyburide in type 2 **diabetes**
AU Marbury, Thomas; Huang, Won-Chin; Strange, Poul; Lebovitz, Harold
CS Private Practice, Orlando Clinical Research Center, Orlando, FL, USA
SO Diabetes Res. Clin. Pract. (1999), 43(3), 155-166
CODEN: DRCPE9; ISSN: 0168-8227
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB This prospective, 1-yr, multicenter, double-blind, randomized, parallel-group study compared the efficacy and safety of repaglinide with glyburide in patients with type 2 **diabetes**. Five hundred and seventy-six patients with type 2 **diabetes** of at least 6 mo' duration were randomized to receive monotherapy with repaglinide (n=383) or glyburide (n=193). During weeks 1-8, **doses** were gradually increased to achieve a target fasting plasma glucose (FPG) **range** of 80-140 mg/dL. The final adjusted **dose** was maintained for 12 mo. Repaglinide patients received a starting **dose** of 0.5 mg three times/day preprandially, adjusted as necessary to 1, 2 or 4 mg before breakfast, lunch and dinner. Glyburide patients received a starting **dose** of 2.5 mg before breakfast and placebo before lunch and dinner. Glyburide was increased as necessary to 5 or 10 mg before breakfast (placebo before lunch and dinner) or to 15 mg (10 mg before breakfast, placebo before lunch, and 5 mg before dinner). After study drug was stopped, patients were transferred to an appropriate **therapy**, as recommended by the investigator. Efficacy was assessed by changes from baseline in glycemic control parameters and in C-peptide, insulin, and lipid profiles. Repaglinide provided glycemic control that was at least as effective and potentially safer than that provided by glyburide. The glucose-lowering effect of repaglinide was most pronounced in pharmacotherapy-naive patients, who showed rapid and marked decreases in mean glycosylated Hb levels from baseline (9.4%) to month 3 (7.6%) and month 12 (7.9%). Mean FPG levels also decreased overall in this group, from 222 mg/dL at baseline, to 175 mg/dL at month 3, to 188 mg/dL at month 12. At endpoint, morning C-peptide levels had increased significantly in glyburide-treated patients compared with those treated with repaglinide, but morning fasting insulin levels did not differ significantly between the two groups. Repaglinide efficacy was sustained over 1 yr and was not influenced by age or sex. Overall safety and changes in lipid profile and body wt. were similar with both agents, with no significant change after extended pharmacotherapy. Wt. gain data for the subset of pharmacotherapy-naive patients suggest that patients given repaglinide may gain less wt. than those given glyburide. Repaglinide, at **doses** of 0.5-4.0 mg administered three times preprandially, was well tolerated and provided safe and consistently effective glycemic control during this 1-yr study. Patients using repaglinide received the same **therapeutic** benefits as those using glyburide, and may have received addnl. benefits.
ST antidiabetic repaglinide glyburide type 2 **diabetes**
IT Antidiabetic agents
(long-term **therapeutic** effectiveness of repaglinide compared with glyburide in type 2 **diabetes**)
IT **10238-21-8**, Glyburide 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(long-term **therapeutic** effectiveness of repaglinide compared with glyburide in type 2 **diabetes**)

L64 ANSWER 21 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 3
AN 1999:97164 HCAPLUS
DN 130:347657

TI Prognostic factors for successful insulin **therapy** in subjects with type 2 **diabetes**

AU Wolffenbuttel, Bruce H. R.; Sels, Jean-Pierre J. E.; Rondas-Colbers, Gabrielle J. W. M.; Menheere, Paul P. C. A.

CS Department of Endocrinology and Metabolism, University Hospital Maastricht, Maastricht, NL-6202 AZ, Neth.

SO Neth. J. Med. (1999), 54(2), 63-69
CODEN: NLJMAV; ISSN: 0300-2977

PB Elsevier Science B.V.

DT Journal

LA English

CC 2-6 (Mammalian Hormones)

AB The objective of the study was to assess which factors influence or predict the efficacy of insulin **therapy** in subjects with type 2 **diabetes**, who were poorly controlled despite maximal **doses** of oral glucose **lowering** agents. Seventy-five patients with type 2 **diabetes** participated (mean age, 67 yr; body mass index, 25.8 kg/M2; median time since diagnosis of **diabetes**, 8 yr (**range** 1-36); 27 males and 48 females). They were transferred to insulin **therapy**, in which case either insulin alone, or a combination of insulin and glibenclamide was employed. The importance of baseline parameters (glycemic control, beta-cell function, measures of insulin resistance) was assessed by comparing good and poor responders (defined as achieved HbA1c <8.0 or >9.0%) to insulin **therapy**, and by multiple logistic regression anal. of these baseline parameters and achieved metabolic control. During insulin **therapy**, HbA1c levels decreased from 10.9 to 8.2%, and fasting blood glucose levels decreased from 14.0 to 8.2 mM. Thirty patients reached HbA1c levels <8.0%, 21 of them even <7.5%. The mean increase in body wt. was 4.5 kg. HbA1c after 6 mo was 7.0% in the good responders, and 9.8% in the poor responders, despite a comparable insulin **dose**. Baseline metabolic control was similar in both groups. Also, glucagon-stimulated and calcd. insulin secretion, as well as parameters of insulin resistance, such as fasting serum insulin levels, free fatty acids, and serum triglycerides, were not different between both groups, and certainly not higher in the poor responders. Also previous metformin use was not different. However, poor responders were more obese than good responders, and had significantly longer known duration of **diabetes**. Multiple logistic regression confirmed that only duration of **diabetes** and body mass index were independent predictors of response to insulin **therapy**. The authors conclude that in elderly patients with type 2 **diabetes** improvement of glycemic control can be achieved at the expense of some wt. gain. Measurement of residual insulin secretion prior to institution of insulin treatment does not discriminate between good and poor responders to this mode of **therapy**. Esp. in obese patients with longer duration of **diabetes** more attention is needed to achieve optimal glycemic control. Combination of insulin with newer drugs, like thiazolidinediones, may perhaps achieve this.

ST insulin **therapy diabetes** type2 blood glucose prognostic factor

IT Obesity
(glycemic control improvement in type 2 **diabetes** insulin **therapy** can be achieved at the expense of some body wt. gain in human)

IT Lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin **therapy** in humans with type 2 **diabetes** has moderate beneficial effect on serum lipoproteins)

IT Insulin resistance
Non-insulin-dependent **diabetes** mellitus
.beta.-Cell
(prognostic factors in relation to insulin resistance and .beta.-cell function for successful insulin **therapy** in humans with type 2

diabetes)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prognostic factors in relation to insulin resistance and .beta.-cell function for successful insulin **therapy** in humans with type 2 **diabetes**)
IT **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(prognostic factors in relation to insulin resistance and .beta.-cell function for successful insulin **therapy** in humans with type 2 **diabetes**)
IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prognostic factors in relation to insulin resistance and .beta.-cell function for successful insulin **therapy** in humans with type 2 **diabetes**)

L64 ANSWER 22 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:566524 HCAPLUS
DN 131:208949
TI A comparison of preconstituted, fixed **combinations** of **low-dose** glyburide plus metformin versus high-**dose** glyburide alone in the treatment of type 2 diabetic patients
AU Erle, G.; Lovise, S.; Stocchiero, C.; Lora, L.; Coppini, A.; Marchetti, P.; Merante, D.
CS Div. Endocrine Metabolic Disease, Diabetes Service, S. Bortolo Hospital, Vicenza, I-36100, Italy
SO Acta Diabetol. (1999), 36(1/2), 61-65
CODEN: ACDAEZ; ISSN: 0940-5429
PB Springer-Verlag
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The effectiveness and safety was assessed and compared of preconstituted, fixed, **combinations** of **low-dose** glyburide plus metformin with higher-**dose** glyburide monotherapy in patients with type 2 **diabetes**. This randomized, double-blind, cross-over study comprised 40 patients. After a 30-day run-in period of dietary treatment, patients received **combined** glyburide (5, 7.5 or 10 mg/day) and metformin (**800**, 1,200 or 1,600 mg/day) as preconstituted, fixed **combinations**, or glyburide alone (5, 10 or 15 mg/day). The **dose** was increased stepwise so as to have 1 (T1), 2 (T2), and 3 (T3) months of treatment for any given regimen (6 mo in total). After 2 wk of washout (T4), the groups were then crossed over (T5, T6, T7 periods). Body wt., fasting blood plasma glucose, HbA1c, blood lactate, total cholesterol and HDL-cholesterol, and triglycerides were measured at the beginning and end of T1 and T5, and end of T2, T3, T6 and T7; postprandial plasma glucose, fasting and postprandial plasma insulin and C-peptide were evaluated at the beginning of T1 and T5, and end of T3 and T7. At these latter time points addnl. assessments included routine clin. chem. measurements, ECG, and ophthalmoscopic examn. Statistical anal. was performed by the paired Student's t-test and anal. of variance for cross-over studies. 33 Patients completed the study. Fasting plasma glucose, postprandial plasma glucose, and HbA1c levels improved during **combined** treatment with glyburide at **lower doses** plus metformin. This effect was achieved without any major change of insulin and C-peptide concns. Circulating lactate concns. increased during the regimen including metformin, but they remained well within the ref. values for normal subjects. Plasma total cholesterol and triglycerides levels remained substantially unchanged throughout the study, whereas HDL-cholesterol concns. increased slightly with glyburide plus metformin **therapy**. Routine clin. chem.

measurements, ECG, and ophthalmoscopic examns. did not change during the study. These results demonstrate that improved metabolic control can be achieved with preconstituted, fixed **combinations** of **low -dose** glyburide plus metformin in patients with type 2 **diabetes**, compared to higher **doses** of the sulfonylurea alone.

ST glyburide metformin NIDDM antidiabetic

IT **Diabetes** mellitus
(non-insulin-dependent; glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

IT Antidiabetic agents
(oral; glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

IT 57-88-5, Cholest-5-en-3-ol (3.beta.)-, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(blood, HDL; glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

IT 50-99-7, D-Glucose, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(blood; glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

IT **657-24-9**, Metformin **10238-21-8**, Glyburide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

IT 50-21-5, biological studies 62572-11-6, Hemoglobin A1c
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(glyburide plus metformin vs. glyburide alone in type 2 **diabetes**)

L64 ANSWER 23 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:464830 HCAPLUS
DN 131:252370
TI Effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats
AU Tanaka, Yasushi; Uchino, Hiroshi; Shimizu, Tomoaki; Yoshii, Hidenori; Niwa, Masataka; Ohmura, Chie; Mitsuhashi, Naomi; Onuma, Tomio; Kawamori, Ryuzo
CS Bunkyo-ku, Hongo, 2-1-1, School of Medicine, Metabolism and Endocrinology, Department of Medicine, Juntendo University, Tokyo, Japan
SO Eur. J. Pharmacol. (1999), 376(1/2), 17-22
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The effects of metformin treatment on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats were examd. Streptozotocin-induced diabetic rats were treated with **low dose** metformin (50-65 mg kg-1 daily) or high dose metformin (500-650 mg kg-1 daily) for 10 wk. While the metformin-untreated diabetic group showed a significant increase of advanced glycation endproducts (6.1-fold in the lens, 1.6-fold in the sciatic nerve, 2.3-fold in the renal cortex, and 1.9-fold in plasma; all $P<0.01$) compared with the healthy control group, both metformin-treated groups had significantly less advanced glycation endproduct deposition. The % decrease in the **diabetes**-induced increase in advanced glycation endproduct formation by **low** and high **dose** metformin treatment was 25% and 72% in the lens (both $P<0.01$), 31% and 42% in the sciatic nerve (both $P<0.05$), and 16% and 33% in the renal cortex

(P<0.05 and P<0.01), resp. However, the plasma advanced glycation endproduct level showed no significant difference from that in the untreated diabetic group, in spite of slight decrease in plasma glucose and glycated Hb levels in the metformin-treated groups. The **diabetes**-induced sciatic nerve conduction velocity deficits were improved by 46% and 42% by **low** and high **dose** metformin treatment, resp. (both P<0.01). These data suggest that metformin may have a direct antiglycative action, which in turn contributes to amelioration of peripheral nerve function. Thus, metformin treatment may be effective in the prevention of diabetic complications through not only lowering plasma glucose, but also directly inhibiting advanced glycation endproduct formation.

ST metformin advanced glycation endproduct nerve antidiabetic

IT Glycoproteins, specific or class
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(AGE (advanced glycosylation end product); effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

IT Antidiabetic agents
(effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

IT Hemoglobins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(glycohemoglobins; effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

IT Nerve
(peripheral; effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats)

L64 ANSWER 24 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 4
AN 1998:715926 HCAPLUS
DN 129:340208
TI Methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide
IN Taylor, Ian L.; Gettys, Thomas
PA Medical University of South Carolina Foundation for Research Development, USA
SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K049-00
ICS A61K038-28; A61K038-08
NCL 424009200
CC 2-6 (Mammalian Hormones)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5830434	A	19981103	US 1997-806203	19970226

AB The present invention provides a method of treating NIDDM in a patient diagnosed with NIDDM by administering to the patient a compd. in a **pharmaceutically** acceptable carrier that reduces hepatic glucose prodn. in the patient by inhibiting hepatic expression of the alpha

subunit of a Gs protein in a liver cell plasma membrane, thereby inhibiting stimulation of cAMP by glucagon, whereby the redn. in hepatic glucose prodn. treats the NIDDM. In particular, the present invention relates to the administration of pancreatic polypeptide or the carboxyl terminal fragment of pancreatic polypeptide, either alone or in **combination** with insulin or an oral hypoglycemic agent to treat NIDDM. Also provided is a method for screening compds. for the ability to treat NIDDM comprising detg. if the compd. decreases hepatic expression of the alpha subunit of a Gs protein in a liver cell plasma membrane, thereby inhibiting the stimulation of cAMP by glucagon, being a compd. with the ability to treat NIDDM. The present invention further provides a kit for treating NIDDM comprising a compd. in a **pharmaceutically** acceptable carrier that decreases hepatic expression of the alpha subunit of the Gs protein in the liver cell plasma membrane, thereby inhibiting stimulation of cAMP by glucagon.

ST noninsulin dependent **diabetes** treatment pancreatic polypeptide; screening compd noninsulin dependent **diabetes** treatment

IT Drug screening
(method for screening compds. for the ability to treat NIDDM by detg. if the compd. decreases hepatic expression of the alpha subunit of a Gs protein in a liver cell plasma membrane)

IT Antidiabetic agents
Liver
Non-insulin-dependent **diabetes** mellitus
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein)

IT Gs proteins
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein)

IT 59763-91-6, Pancreatic polypeptide 111274-30-7, Pancreatic polypeptide (Canis familiaris)
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein)

IT 9007-92-5, Glucagon, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein which in turn inhibits stimulation of cAMP by glucagon)

IT 60-92-4, CAMP
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein which in turn inhibits stimulation of cAMP by glucagon)

IT 64-77-7, Tolbutamide 94-20-2, Chlorpropamide **657-24-9**, Metformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 9004-10-8, Insulin, biological studies **10238-21-8**, Glyburide 29094-61-9, Glipizide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide in **combination** with insulin or hypoglycemic agents)

IT 192432-73-8
RL: BAC (Biological activity or effector, except adverse); BIOL

(Biological study)
(pancreatic polypeptide fragment; methods of treating non-insulin dependent **diabetes** mellitus with pancreatic polypeptide by inhibiting hepatic expression of the alpha subunit of a Gs protein)

L64 ANSWER 25 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:7821 HCAPLUS
DN 130:47488
TI Novel NIDDM regimen with short-acting oral hypoglycemic agent
IN Hemmingsen, Lisbeth Tofte; Muller, Peter Giortz
PA Novo Nordisk A/S, Den.
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-445
ICS A61K031-47; A61K031-195; A61K031-15
CC 1-10 (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9856378	A1	19981217	WO 1998-DK248	19980612
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9805126	A	19981214	ZA 1998-5126	19980612
AU 9879068	A1	19981230	AU 1998-79068	19980612
PRAI DK 1997-694	19970613			
US 1997-63368	19971029			
WO 1998-DK248	19980612			

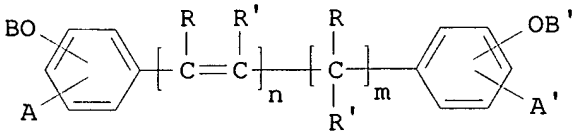
AB The invention relates to the use of a short-acting oral hypoglycemic agent and to a novel regimen in the treatment of type 2 **diabetes** in which the endogenous secretion of insulin is stimulated in connection with meals by administering in connection with the meals a short-acting oral hypoglycemic agent. The invention also relates to a method of achieving significantly improvement in the glycemic control by a **combined** use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.
ST short acting oral hypoglycemic meal NIDDM; antidiabetic short acting oral hypoglycemic meal; repaglinide metformin **combination** antidiabetic NIDDM
IT High-density lipoproteins
Low-density lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cholesterol; short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)
IT Diet
(meals; short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)
IT Antidiabetic agents
Capsules (drug delivery systems)
Drug delivery systems
Non-insulin-dependent **diabetes** mellitus
Pharmacokinetics
Synergistic drug interactions
Tablets (drug delivery systems)
(short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)

IT Glycerides, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)
IT 64-77-7, Tolbutamide 94-20-2, Chlorpropamide **657-24-9**, Metformin **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide 26944-48-9, Glibornuride 29094-61-9, Glipizide 33342-05-1, Gliquidone 97322-87-7, Troglitazone 105816-04-4, A 4166 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)
IT 50-99-7, Glucose, biological studies 57-88-5, Cholesterol, biological studies 4429-04-3, Fructosamine 9004-10-8, Insulin, biological studies 59112-80-0, C-Peptide 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(short-acting oral hypoglycemic agent in NIDDM regimen, and **combinations** with long-acting hypoglycemic agents)

L64 ANSWER 26 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:239103 HCAPLUS
DN 128:290238
TI Use of bisphenolic compounds to treat type II **diabetes**
IN Khandwala, Atul S.; Luo, Jian
PA Shaman Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-05
CC 1-10 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9815266	A1	19980416	WO 1997-US18109	19971006
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5827898	A	19981027	US 1996-726591	19961007
AU 9850795	A1	19980505	AU 1998-50795	19971006
EP 954297	A1	19991110	EP 1997-913665	19971006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1996-726591 19961007
WO 1997-US18109 19971006
OS MARPAT 128:290238
GI



I

AB Methods are provided for treatment of non-insulin-dependent **diabetes** mellitus, for reducing blood glucose levels, or hyperglycemia. The methods entail administering to a mammal in need of

such treatment a therapeutically effective amt. of a **compn.** whose active ingredient consists essentially of a compd. I [R, R' = H, (un)substituted C1-C20 alkyl, (un)substituted C2-C20 alkenyl, or R and R' together form cycloalk(en)yl ring; (C(R):C(R')), (C(R)(R')) are the same or different; A, A' = C2-C20 acylamino, C2-C20 acyloxy, C2-C20 alcanoyl, etc.; B, B' = H, C2-C20 alkanoyl, C3-C20 alkenoyl, C2-C20 alkenyl, etc.; n, m = 0-6] or a **pharmaceutically** acceptable salt thereof. Also provided are methods of treatment using a bisphenolic compd. in conjunction with another hypoglycemic or hypolipidemic agent. The hypoglycemic activity of nordihydroguaiaretic acid is described.

ST bisphenolic compd antidiabetic hypoglycemic; nordihydroguaiaretic acid hypoglycemic

IT Antidiabetic agents
Glucose transport
Hypolipemic agents
(bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

IT .beta.-Adrenoceptor antagonists
(.beta.3-adrenoceptor antagonists; bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 500-38-9, Nordihydroguaiaretic acid 504-78-9D, Thiazolidine, derivs. **657-24-9**, Metformin 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 9004-10-8, Insulin, biological studies **10238-21-8**, Glyburide 21187-98-4, Gliclazide 27686-84-6 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 97322-87-7, Troglitazone 103185-28-0 119584-39-3 119584-40-6
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

IT 74315-95-0, .alpha.-Glycosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; bisphenolic compds. to treat type II **diabetes**, and **combinations** with other agents)

L64 ANSWER 27 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1998-448966 [39] WPIDS
CR 1997-044618 [05]
DNN N1998-350139 DNC C1998-136181
TI Use of insulin sensitivity enhancer e.g. pioglitazone with e.g. biguanide or insulin secretion enhancer - to prevent or treat diabetes and diabetic complications e.g. diabetic neuropathy, nephropathy, retinopathy and osteopaenia.
DC B03
IN IKEDA, H; ODAKA, H; SOHDA, T
PA (TAKE) TAKEDA CHEM IND LTD
CYC 17
PI EP 861666 A2 19980902 (199839)* EN 17p A61K045-06
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
ADT EP 861666 A2 Div ex EP 1996-304570 19960620, EP 1998-200252 19960620
FDT EP 861666 A2 Div ex EP 749751
PRAI JP 1995-153500 19950620
IC ICM A61K045-06

AB EP 861666 A UPAB: 19981028
A composition comprising an insulin sensitivity enhancer in combination with an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, an LDL catabolism enhancer and/or an ACE inhibitor, is new. Also claimed is a compound of formula (II) or a salt in combination with an insulin secretion enhancer and/or an insulin preparation. R' = optionally substituted hydrocarbon or heterocycle; Y = CO, CH(OH) or NR3; R3 = optionally substituted alkyl; m = 0 or 1; n = 0-2; X = CH or N; A = bond or 1-7C divalent aliphatic hydrocarbon; Q = O or S; R1 = hydrogen or 1-10C alkyl; E has 0-4 substituents (optionally combined with R1 to form a ring); L, M = H; or L+M = bond; provided that R is not benzopyranyl when m and n = 0, X = CH, A = bond, Q = S, R1, L and M = H and E does not have further substituents.
USE - The compositions are used for prevention or treatment of diabetes (claimed) and diabetic complications e.g. diabetic neuropathy, nephropathy, retinopathy, macroangiopathy and osteopaenia. The insulin sensitivity enhancers are administered orally at a dosage of 0.01-10 (preferably 0.05-5) mg/kg or parenterally at a dosage of 0.005 to 10 (preferably 0.01-1) mg/kg in up to 3 daily doses.
ADVANTAGE - The compositions can achieve stable hypoglycaemic efficacy in long-term therapy with low risk of side effects.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B04-M01; B07-D04C; B07-E01; B07-F01; B14-F02B1; B14-S04

L64 ANSWER 28 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:37675 HCAPLUS
DN 130:232289
TI Efficacy of **low-dose** metformin in Japanese patients with type 2 **diabetes** mellitus
AU Ohmura, Chie; Tanaka, Yasushi; Mitsuhashi, Naomi; Atsum, Yoshihito; Matsuoka, Kenpei; Onuma, Tomio; Kawamori, Ryuzo
CS Department of Medicine, Metabolism and Endocrinology, School of Medicine, Juntendo University, Tokyo, 113-8421, Japan
SO Curr. Ther. Res. (1998), 59(12), 889-895
CODEN: CTCEA9; ISSN: 0011-393X
PB Excerpta Medica
DT Journal
LA English
CC 1-10 (Pharmacology)
AB This study examd. the antihyperglycemic effect of **low-dose** metformin in nonobese and obese Japanese patients with type 2 **diabetes** mellitus. Metformin (500-750 mg daily) was given as monotherapy or in **combination** with a sulfonylurea. After 6 mo of treatment, the fasting plasma glucose level had decreased from 190 mg/dL to 155 and the glycated Hb A1c level from 8.8% to 7.4% in the monotherapy group. These same variables decreased from 218 mg/dL 162 mg/dL and from 9.5% to 8.4% in the **combination therapy** group. Thus, even **low doses** of metformin can improve hyperglycemia in Japanese patients with type 2 **diabetes** mellitus.
ST metformin sulfonylurea **diabetes** treatment; antidiabetic metformin sulfonylurea
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(**low-dose** metformin effects in Japanese patients with type 2 **diabetes** mellitus)
IT Obesity
(**low-dose** metformin effects in Japanese patients with type 2 **diabetes** mellitus and)
IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(**low-dose** metformin plus sulfonylureas effects in Japanese patients with type 2 **diabetes** mellitus)

IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**low-dose** metformin plus sulfonylureas effects in Japanese patients with type 2 **diabetes** mellitus in relation to effects on)

IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of **low-dose** metformin in Japanese patients with type 2 **diabetes** mellitus)

IT **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**low-dose** metformin plus sulfonylureas effects in Japanese patients with type 2 **diabetes** mellitus)

IT 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**low-dose** metformin plus sulfonylureas effects in Japanese patients with type 2 **diabetes** mellitus in relation to effects on glycated)

IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**low-dose** metformin plus sulfonylureas effects in Japanese patients with type 2 **diabetes** mellitus in relation to effects on plasma)

L64 ANSWER 29 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:637636 HCAPLUS
DN 130:32878
TI Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 **diabetes** (UKPDS 34)
CS UK Prospective Diabetes Study (UKPDS) Group, Diabetes Research Laboratories, Radcliffe Infirmary, Oxford, OX2 6HE, UK
SO Lancet (1998), 352(9131), 854-865
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet Ltd.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB In patients with type 2 **diabetes**, intensive blood-glucose control with insulin or sulfonylurea therapy decreases progression of microvascular disease and may also reduce the risk of heart attacks. This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage. Of 4075 patients recruited to UKPDS in 15 centers, 1704 overweight (>120% ideal bodyweight) patients with newly diagnosed type 2 **diabetes**, mean age 53 yr, had raised fasting plasma glucose (FPG; 6.1-15.0 mmol/L) without hyperglycemic symptoms after 3 mo' initial diet. 753 Were included in a randomized controlled trial, median duration 10.7 yr, of conventional policy, primarily with diet alone (n=411) vs. intensive blood-glucose control policy with metformin, aiming for FPG below 6 mmol/L (n=342). A secondary anal. compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). The primary outcome measures were aggregates of any **diabetes**-related clin. endpoint, **diabetes**-related death, and all-cause mortality. In a supplementary randomized controlled trial, 537 non-overweight and overweight patients, mean age 59 yr, who were already on max. sulfonylurea therapy but had raised FPG (6.1-15.0 mmol/L) were allocated continuing sulfonylurea therapy alone (n=269) or addn. of metformin (n=268). Median glycated Hb (HbA1c) was 7.4% in the metformin group compared with 8.0% in the conventional group. Patients allocated metformin, compared with the

conventional group, had risk redns. of 32% (95% Cl 13-47, p=0.002) for any **diabetes**-related endpoint, 42% for **diabetes**-related death (9-63, p=0.017), and 36% for all-cause mortality (9-55, p=0.011). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any **diabetes**-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032). Early addn. of metformin in sulfonylurea-treated patients was assocd. with an increased risk of **diabetes**-related death (96% increased risk [95% Cl 2-275], p=0.039) compared with continued sulfonylurea alone. A **combined** anal. of the main and supplementary studies showed fewer metformin-allocated patients having **diabetes**-related endpoints (risk redn. 19% [2-33], p=0.033). Epidemiol. assessment of the possible assocn. of death from **diabetes**-related causes with the concurrent therapy of **diabetes** in 4416 patients did not show an increased risk in **diabetes**-related death in patients treated with a **combination** of sulfonylurea and metformin (risk redn. 5% [- 33 to 32], p=0.78). Since intensive glucose control with metformin appears to decrease the risk of **diabetes**-related endpoints in overweight diabetic patients, and is assocd. with less wt. gain and fewer hypoglycemic attacks than are insulin and sulfonylureas, it may be the first-line pharmacol. therapy of choice in these patients.

ST metformin **diabetes** NIDDM blood glucose overweight

IT Antidiabetic agents
Body weight
Non-insulin-dependent **diabetes** mellitus
(metformin intensive blood-glucose control effects on complications in overweight humans with NIDDM)

IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metformin intensive blood-glucose control effects on complications in overweight humans with NIDDM)

IT 94-20-2, Chlorpropamide **657-24-9**, Metformin **10238-21-8**, Glibenclamide
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin intensive blood-glucose control effects on complications in overweight humans with NIDDM)

IT 9004-10-8, Insulin, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin intensive blood-glucose control effects on complications in overweight humans with NIDDM)

L64 ANSWER 30 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:159739 HCAPLUS
DN 130:246798
TI Efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas. Is it predictable?
AU Trischitta, V.; Italia, S.; Raimondo, M.; Guardabasso, V.; Licciardello, C.; Runello, F.; Mazzarino, S.; Sangiorgi, L.; Anello, M.; Vigneri, R.
CS Divisione ed Unita di Ricerca di Endocrinologia, Istituto Scientifico Casa Sollievo della Sofferenza, San Giovanni Rotondo, 71013, Italy
SO J. Endocrinol. Invest. (1998), 21(11), 744-747
CODEN: JEIND7; ISSN: 0391-4097
PB Editrice Kurtis s.r.l.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The treatment of NIDDM patients with secondary failure to sulfonylurea is a common problem. We performed a crossover study in 50 NIDDM patients with secondary failure to glibenclamide by comparing the addn. to sulfonylurea of either a **low-dose** bedtime NPH insulin or a t.i.d. oral metformin and by analyzing treatment efficacy in relation

to patient and disease characteristics. Both **combined therapies** clearly improved glycemic control. HbA1c were similarly reduced by the addn. of either bedtime NPH insulin (7.6.+-.0.34 vs 8.7.+-.0.35, p<0.01) or metformin (7.6.+-.0.22 vs 8.6.+-.0.31, p<0.01). Also fasting plasma glucose (FPG) and post-prandial plasma glucose (PPPG) significantly decreased (p<0.01) with both treatments. Bedtime NPH insulin was more effective on FPG redn. than metformin (-36.+-.2% vs -25.+-.2%, p<0.01); in contrast, metformin addn. was more effective on PPPG redn. than bedtime NPH insulin addn. (-30.+-.2% vs 20.+-.3%, p<0.01). Serum cholesterol was marginally but significantly decreased after metformin (5.49.+-.0.19 vs 5.91.+-.0.18 mM, p<0.05) but not after NPH insulin. Body wt. increase was significantly greater after insulin addn. than after metformin (1.47.+-.0.25 Kg vs 0.64.+-.0.17 p=0.02). All patients preferred the addn. of metformin rather than NPH insulin. None of the measured clin. and metabolic variables (before treatment FPG and PPPG, HbA1c, post-glucagon C-peptide levels, insulin sensitivity, patient age, BMI and **diabetes** duration) significantly correlated to the efficacy of the two **combined** treatments studied. In conclusion, in NIDDM patients with secondary failure to sulfonylureas the addn. of either **low-dose** bedtime NPH insulin or t.i.d. metformin is similarly effective in improving glycemic control. Metformin is better accepted by patients and provides a modest advantage in terms of body wt. and cholesterol levels. The most common clin. and metabolic variables are not useful for predicting the efficacy of these two **combined** treatments.

ST sulfonylurea NPH insulin glibenclamide metformin **diabetes**

IT Antidiabetic agents
Body weight
Non-insulin-dependent **diabetes** mellitus
(efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas)

IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas)

IT **657-24-9**, Metformin 9004-17-5, NPH insulin **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas)

IT 57-88-5, Cholesterol, biological studies 62572-11-6, Hemoglobin A1c
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(efficacy of **combined** treatments in NIDDM patients with secondary failure to sulfonylureas)

L64 ANSWER 31 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:599599 HCAPLUS
DN 131:208932
TI **Combined** glibenclamide plus metformin improves insulin sensitivity in non-obese Type 2 diabetic patients
AU Pastore, L.; Morviducci, L.; Merante, D.; Coppini, A.; Mellozzi, M.; D'Adamo, M.; Sbraccia, P.; Giaccari, A.; Tamburrano, G.
CS Division of Endocrinology, II Institute of Medicine, University of Rome "La Sapienza", Rome, I-00161, Italy
SO Diabetes, Nutr. Metab. (1998), 11(4), 225-231
CODEN: DNMEEW; ISSN: 0394-3402
PB Editrice Kurtis s.r.l.
DT Journal

LA English
CC 1-10 (Pharmacology)
AB The aim of this study was to evaluate the efficacy of a treatment with metformin (alone or **combined** with a sulfonylurea) on glycemic control and insulin sensitivity in non-obese patients with Type 2 **diabetes** mellitus already treated with sulfonylureas alone. Fifteen non-obese (BMI < 30 kg/m2) patients already satisfactorily treated (HbA1c <7.5%) with sulfonylureas were studied. Patients were first switched to glibenclamide alone for at least one month, then blindly divided into 3 groups: metformin, glibenclamide, and metformin + glibenclamide. Insulin sensitivity was evaluated before, and after one month, with the steady state plasma glucose concn. reached after a const. infusion of glucose, insulin and octreotide (SSPG). Fasting and post-breakfast glucose, insulin and C-peptide were also assayed. Patients' clin. data were similar in the three groups (BMI: 27.1.+-.0.6 kg/m2; HbA1c: 7.2.+-.0.5 %; fasting glycemia: 8.8.+-.0.8 mmol/l; post-prandial glycemia: 10.9.+-.1.1 mmol/l). SSPG, similar before the study (9.31.+-.0.12 mmol/l), significantly improved in patients treated with **combined** therapy (7.56.+-.0.42), worsened in patients switched to metformin (11.9.+-.0.56). BMI remained unchanged in the three groups; fasting glycemia decreased slightly in patients treated with **combined** therapy and increased in patients treated with metformin. These results demonstrate that metformin, **combined** with glibenclamide, improves peripheral insulin sensitivity. Taking into account the pivotal role of insulin resistance in Type 2 **diabetes** mellitus, a therapeutic protocol of assocn. (sulfonylurea + metformin) could be suggested as first choice even in non-obese diabetic patients.
ST glibenclamide metformin antidiabetic glucose insulin NIDDM
IT Antidiabetic agents
(NIDDM; **combined** glibenclamide plus metformin improves insulin sensitivity in non-obese type 2 diabetic humans)
IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(blood; **combined** glibenclamide plus metformin improves insulin sensitivity in non-obese type 2 diabetic humans)
IT **657-24-9**, Metformin **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**combined** glibenclamide plus metformin improves insulin sensitivity in non-obese type 2 diabetic humans)
IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**combined** glibenclamide plus metformin improves insulin sensitivity in non-obese type 2 diabetic humans)

L64 ANSWER 32 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 2000038204 EMBASE
TI Effects of insulin-oral hypoglycemic agents combined therapy in outpatients with type 2 diabetes.
AU Sinagra D.; Scarpitta A.M.; Amato M.
CS D. Sinagra, Istituto di Clinica Medica I, Div. Endocrinol. e Malat. Ricambio, Policlinico Univ. 'Paolo Giaccone', Palermo, Italy
SO European Review for Medical and Pharmacological Sciences, (1998) 2/5-6 (175-179).
Refs: 20
ISSN: 0392-291X CODEN: RESFDJ
CY Italy
DT Journal; Article
FS 006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB To evaluate the efficacy of combined insulin-OHAs therapy in subjects with

NIDDM who received treatment with OHAs and insulin alone, we selected 80 outpatients divided in two groups: Group A: 38 subjects treated with OHAs therapy that received insulin treatment for secondary failure; Group B: 24 subjects in which OHAs therapy was added to insulin regimen to avoid the effects of hyperinsulinization. In the group A body weight increased significantly (+1.94 .+-. 2.80 kg, p< 0.001 vs baseline), while in group B no gain of body weight was observed. Both groups showed a similar improvement of glycemic control. For the group A, the FPG and HbA1c decreased, respectively, from 14.84 .+-. 3.76 to 8.72 .+-. 2.92 mmol/l and from 9.10 .+-. 0.30 to 7.20 .+-. 0.53% at 6 months (p< 0.001). For the group B FPG and HbA1c decreased, respectively, from 12.05 .+-. 3.49 to 8.24 .+-. 3.01 mmol/l and from 8.3 .+-. 0.1 to 8.8 .+-. 0.13% (p< 0.001). Plasma cholesterol, triglycerides and uric acid concentrations did not show significant changes in either group. Insulin requirement in group A was 0.21 .+-. 0.13 U/Kg/day. Despite of improvement of glycemia, total insulin requirement decreased in Group B from 0.53 .+-. 0.25 to 0.34 .+-. 0.2 U/Kg/day after OHAs therapy (p< 0.001). In the group A the bedtime insulin administration was prevalent (52.88%), while the most patients of group B needed a second or a third daily insulin injection (83.33%). In conclusion, in type 2 diabetic patients, therapy with combination of OHAs and insulin was associated with **lower** insulin **doses** and less weight gain.

CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
combination chemotherapy
insulin treatment
drug efficacy
outpatient care
cholesterol blood level
triacylglycerol blood level
uric acid blood level
human
male
female
major clinical study
controlled study
aged
adult
article
Drug Descriptors:
***oral antidiabetic agent: CB, drug combination**
*oral antidiabetic agent: DT, drug therapy
***insulin: CB, drug combination**
*insulin: DT, drug therapy
cholesterol: EC, endogenous compound
uric acid: EC, endogenous compound
triacylglycerol: EC, endogenous compound
hemoglobin A1c: EC, endogenous compound
glibenclamide: CB, drug combination
glibenclamide: DT, drug therapy
gliclazide: CB, drug combination
gliclazide: DT, drug therapy
metformin: CB, drug combination
metformin: DT, drug therapy

RN (insulin) 9004-10-8; (cholesterol) 57-88-5; (uric acid) 69-93-2; (hemoglobin A1c) 62572-11-6; (glibenclamide) **10238-21-8;** (gliclazide) 21187-98-4; (metformin) **1115-70-4, 657-24-9**

L64 ANSWER 33 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:571669 HCAPLUS
DN 129:315463
TI Folate administration reduces circulating homocysteine levels in NIDDM patients on long-term metformin treatment
AU Aarsand, A. K.; Carlsen, S. M.

CS Faculty of Medicine, Department of Medicine, University Hospital of Trondheim, Norwegian University of Science and Technology, Trondheim, Norway
SO J. Intern. Med. (1998), 244(2), 169-174
CODEN: JINMEO; ISSN: 0954-6820
PB Blackwell Science Ltd.
DT Journal
LA English
CC 18-2 (Animal Nutrition)
Section cross-reference(s): 1
AB Metformin treatment increases circulating homocysteine levels. We studied whether administration of folate reduces serum total homocysteine levels in patients on long-term metformin treatment. Thirty patients treated with a metformin **dose** of at least 1000 mg day-1 for a min. of 1 yr were included in a prospective, randomized, double-blind, placebo-controlled study lasting for 12 wk and taking place in a university hospital setting. At baseline serum total homocysteine levels were within the ref. **range**. One patient who withdrew and one who died were excluded from the statistical evaluation. Twenty-six of the remaining patients suffered from NIDDM, the other two from hyperlipidemia. Patients were randomized into two groups at week 0. The folate group received 0.25 mg day-1 of folate in addn. to 60 mg day-1 of Fe2+, while the placebo group received only 60 mg day-1 of Fe2+. Fasting homocysteine, cysteine, cysteinylglycine, vitamin B12 and folate were measured at week 0, 4 and 12. Changes from week 0 to week 4 and from week 0 to week 12 were calcd. Folate administration reduced serum levels of total homocysteine in the folate group as compared with the placebo group by 13.9% ($P < 0.01$) and 21.7% ($P < 0.001$) at week 4 and 12, resp. In the folate group vs. the placebo group serum levels of vitamin B12 increased by 9.9% ($P = 0.010$) and 9.6% ($P = 0.043$) while folate levels increased by 96.9 and 89.9% at week 4 and 12, resp. The present study indicates that the homocysteine-increasing effect of metformin can be counteracted by folate administration.
ST folate homocysteine NIDDM metformin
IT Non-insulin-dependent **diabetes** mellitus
(folate corrects metformin-induced hyperhomocysteinema in humans with NIDDM)
IT 59-30-3, Folic acid, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(folate corrects metformin-induced hyperhomocysteinema in humans with NIDDM)
IT **657-24-9**, Metformin
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(folate corrects metformin-induced hyperhomocysteinema in humans with NIDDM)
IT 52-90-4, Cysteine, biological studies 68-19-9, Vitamin B12 6027-13-0, L-Homocysteine 19246-18-5, Cysteinylglycine
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(folate corrects metformin-induced hyperhomocysteinema in humans with NIDDM)

L64 ANSWER 34 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 1998020371 EMBASE
TI Management of dyslipidemia in adults with diabetes.
AU Haffner S.M.
CS Dr. S.M. Haffner, Department of Medicine, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-7873, United States
SO Diabetes Care, (1998) 21/1 (160-178).
Refs: 235
ISSN: 0149-5992 CODEN: DICAD2

CY United States
DT Journal; General Review
FS 003 Endocrinology
006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Subjects with diabetes have a greatly increased risk of CHD, which is only partially related to their elevated glucose. Other factors such as insulin resistance and dyslipidemia are likely to be important. The type of dyslipidemia that is most characteristic of type 2 diabetic subjects is elevated triglycerides and decreased HDL cholesterol levels, although all lipoproteins have compositional abnormalities. Surprisingly few good prospective studies of lipoprotein levels in relation to CHD have been done in diabetic subjects. Available studies suggest that low HDL cholesterol may be the most important risk factor for CHD in observational studies. In studies in which total cholesterol and triglyceride were done, cholesterol and triglycerides were risk factors for CHD, although triglycerides were often a stronger predictor. However, the strength of triglyceride as a risk factor for CHD may depend partially on its association with other variables (e.g., hypertension, plasminogen activator inhibitor 1 [PAI-1], etc.). In clinical trials in diabetic subjects, LDL reduction with statins has led to significant reductions in CHD incidence. In addition, overall mortality was reduced with statin therapy, although the results were not statistically significant. Gemfibrozil has led to reductions in CHD incidence in diabetic subjects, although the results were not statistically significant perhaps because of low sample size. Regarding lipoproteins and CHD risk in diabetic patients, the very positive results of statin trials point to LDL cholesterol being more important than previously realized. Apparently, having a borderline high LDL cholesterol (between 130 and 160 mg/dl) in a diabetic patient is equivalent to a much higher LDL cholesterol in terms of CHD risk for a nondiabetic subject. Therefore, the primary target of therapy in diabetic patients is lowering LDL cholesterol (or possibly, non-HDL cholesterol). Statins are the preferred pharmacological agent in this situation. Once LDL cholesterol levels have been lowered, attention can be given to treatment of residual hypertriglyceridemia and low HDL. The goal here is weight reduction and increased exercise. However, for selected patients, combining a fibric acid (or **low-dose** nicotinic acid)
with a statin also can be considered. Reduction of LDL levels should take priority over reduction of triglycerides in combined hyperlipidemia because of the proven safety of the statin class of drugs as well as greater reduction in CHD incidence.
CT Medical Descriptors:
*dyslipidemia: DM, disease management
*dyslipidemia: DT, drug therapy
*dyslipidemia: EP, epidemiology
*dyslipidemia: TH, therapy
*ischemic heart disease: CO, complication
*ischemic heart disease: EP, epidemiology
***non insulin dependent diabetes mellitus: DT, drug therapy**
***non insulin dependent diabetes mellitus: EP, epidemiology**
***non insulin dependent diabetes mellitus: TH, therapy**
insulin dependent diabetes mellitus: DT, drug therapy
insulin dependent diabetes mellitus: EP, epidemiology
hyperglycemia
glucose homeostasis
atherosclerosis
insulin resistance
diet therapy
kinesiotherapy
cost effectiveness analysis

gastrointestinal symptom: SI, side effect
liver toxicity: SI, side effect
rhabdomyolysis: SI, side effect
drug mixture
human
male
female
major clinical study
clinical trial
randomized controlled trial
double blind procedure
multicenter study
controlled study
review
Drug Descriptors:
*lipid: EC, endogenous compound
*lipoprotein: EC, endogenous compound
*hydroxymethylglutaryl coenzyme a reductase inhibitor: CT, clinical trial
*hydroxymethylglutaryl coenzyme a reductase inhibitor: DO, drug dose
*hydroxymethylglutaryl coenzyme a reductase inhibitor: DT, drug therapy
*hydroxymethylglutaryl coenzyme a reductase inhibitor: PD, pharmacology
*antilipemic agent: CT, clinical trial
*antilipemic agent: DO, drug dose
*antilipemic agent: DT, drug therapy
*antilipemic agent: PD, pharmacology
*bile acid: AE, adverse drug reaction
*bile acid: DT, drug therapy
*bile acid: PD, pharmacology
*nicotinic acid: AE, adverse drug reaction
*nicotinic acid: DT, drug therapy
*nicotinic acid: PD, pharmacology
tolbutamide: CT, clinical trial
tolbutamide: DT, drug therapy
insulin: CT, clinical trial
insulin: DT, drug therapy
metformin: CT, clinical trial
metformin: DT, drug therapy
chlorpropamide: CT, clinical trial
chlorpropamide: DT, drug therapy
glibenclamide: CT, clinical trial
glibenclamide: DT, drug therapy
acarbose: CT, clinical trial
acarbose: DT, drug therapy
simvastatin: CT, clinical trial
simvastatin: CB, drug combination
simvastatin: DO, drug dose
simvastatin: DT, drug therapy
simvastatin: PR, pharmaceutics
simvastatin: PD, pharmacology
sulfonylurea derivative: CT, clinical trial
sulfonylurea derivative: DT, drug therapy
gemfibrozil: AE, adverse drug reaction
gemfibrozil: CB, drug combination
gemfibrozil: DO, drug dose
gemfibrozil: DT, drug therapy
gemfibrozil: EC, endogenous compound
gemfibrozil: PD, pharmacology
resin: AE, adverse drug reaction
resin: DO, drug dose
resin: DT, drug therapy
resin: EC, endogenous compound
resin: PD, pharmacology
pravastatin: CT, clinical trial
pravastatin: CB, drug combination

pravastatin: DO, drug dose
pravastatin: DT, drug therapy
pravastatin: EC, endogenous compound
pravastatin: PD, pharmacology
cholesterol: EC, endogenous compound
mevinolin: CT, clinical trial
mevinolin: CB, drug combination
mevinolin: DO, drug dose
mevinolin: DT, drug therapy
mevinolin: PD, pharmacology
fenofibrate: CT, clinical trial
fenofibrate: DO, drug dose
fenofibrate: DT, drug therapy
fenofibrate: PD, pharmacology
fibric acid derivative: CB, drug combination
fibric acid derivative: DO, drug dose
fibric acid derivative: DT, drug therapy
fibric acid derivative: PD, pharmacology
triacylglycerol
low density lipoprotein
high density lipoprotein
lipoprotein a

RN (lipid) 66455-18-3; (nicotinic acid) 54-86-4, 59-67-6; (tolbutamide) 473-41-6, 64-77-7; (insulin) 9004-10-8; (metformin) **1115-70-4**, **657-24-9**; (chlorpropamide) 94-20-2; (glibenclamide) **10238-21-8**; (acarbose) 56180-94-0; (simvastatin) 79902-63-9; (gemfibrozil) 25812-30-0; (pravastatin) 81131-74-0; (cholesterol) 57-88-5; (mevinolin) 75330-75-5; (fenofibrate) 49562-28-9

L64 ANSWER 35 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:163857 HCAPLUS
DN 128:213123
TI Effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metabolism and protein phosphorylation in non insulin dependent **diabetes** mellitus
AU Itaya, Satomi; Ishizuka, Tatsuo; Wada, Hiroaki; Miura, Atsushi; Kanoh, Yoshinori; Ishizawa, Masayoshi; Yasuda, Keigo
CS Sch. Med., Gifu Univ., Gifu, 500, Japan
SO Gifu Daigaku Igakubu Kiyo (1998), 46(1), 26-33
CODEN: GDIKAN; ISSN: 0072-4521
PB Gifu Daigaku Igakubu
DT Journal
LA Japanese
CC 1-10 (Pharmacology)
AB It has been reported that increased platelet aggregation is assocd. with the development of diabetic complications. We examd. the effect of alterations in diabetic treatments, from diet alone into sulfonylurea (glyburide) and from sulfonylurea into insulin, on platelet aggregation, phosphoinositide metab. and protein phosphorylation in patient with NIDDM. **Low-dose** thrombin-stimulated platelet aggregation and phosphatidic acid (PA) formation was suppressed by the alteration of diet alone into sulfonylurea administration. Moreover, substitution of insulin treatment for sulfonylurea administration resulted in decreases in ADP-, collagen- and thrombin-stimulated platelet aggregation, and thrombin-induced PA formation. In conclusion, both sulfonylurea and insulin treatments suppress the platelet aggregation via suppression of thrombin-induced activation of phosphoinositide metab.
ST antidiabetic thrombin platelet aggregation phosphoinositide phosphorylation
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
Platelet aggregation inhibitors
Protein phosphorylation
(effects of changing diabetic treatment on thrombin-induced platelet

aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

IT Phosphoinositides
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

IT Phosphatidic acids
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

IT 9002-04-4, Thrombin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

IT 9004-10-8, Insulin, biological studies **10238-21-8**, Glyburide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effects of changing diabetic treatment on thrombin-induced platelet aggregation, phosphoinositide metab. and protein phosphorylation in non insulin dependent **diabetes** mellitus)

L64 ANSWER 36 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 5
AN 1997:421346 HCAPLUS
DN 127:39859
TI A glibenclamide-metformin **combination** for the treatment of **diabetes** mellitus type II.
IN Barelli, Giulio; De, Regis Massimo
PA Istituto Gentili S.P.A., Italy; Barelli, Giulio; De Regis, Massimo
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-64; A61K031-155
CC 63-6 (**Pharmaceuticals**)
Section cross-reference(s): 1, 2

prior art

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9717975	A1	19970522	WO 1996-EP4860	19961107
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2237571	AA	19970522	CA 1996-2237571	19961107
AU 9675668	A1	19970605	AU 1996-75668	19961107
EP 869796	A1	19981014	EP 1996-938124	19961107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

US 5922769 A 19990713 US 1998-29371 19980513
PRAI IT 1995-MI2337 19951114
WO 1996-EP4860 19961107
AB The use of a **combination** of glibenclamide and metformin (1:100) for the prepn. of a single dose medicament useful for the treatment of **diabetes** mellitus type II is disclosed, thus avoiding the insulin therapy in the most severe cases. Thus, suspensions contained 10.100, metformin-HCl 0.047, sodium CM-cellulose 0.079, microcryst. cellulose 0.300, wild black cherry essence 0.089, anise essence 0.050, glycerol 10.000, Me p-hydroxybenzoate 0.050, ans saccharose 77.47 g, and water q.s. to 100 mL.
ST glibenclamide metformin **diabetes** mellitus type II; antidiabetic glibenclamide metformin
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(glibenclamide-metformin **combination** for treatment of **diabetes** mellitus of type ii.)
IT **657-24-9**, Metformin **1115-70-4**, Metformin hydrochloride **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glibenclamide-metformin **combination** for treatment of **diabetes** mellitus of type ii.)

L64 ANSWER 37 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1998-050960 [05] WPIDS
DNC C1998-017351
TI Purified tri terpenoid derivatives - hypoglycaemic agents used for treating insulin dependent and non-insulin dependent diabetes.
DC B05
IN INMAN, W D; REED, M J
PA (SHAM-N) SHAMAN PHARM INC
CYC 1
PI US 5691386 A 19971125 (199805)* 8p A61K031-12
ADT US 5691386 A US 1996-633396 19960416
PRAI US 1996-633396 19960416
IC ICM A61K031-12
AB US 5691386 A UPAB: 19980202
Purified triterpenoid derivatives of formula (I) and their salts are new. Also claimed is a composition comprising (I) for use as a hypoglycaemic.
USE - (I) are hypoglycaemic agents used for reducing blood sugar and treating diabetes (claimed) i.e. insulin-dependent and/or non-insulin dependent diabetes. It can reduce the blood glucose level due to acute stress such as experienced by patients with hyperthermia, trauma, sepsis and burns and undergoing general anaesthesia. They are used to treat hyperglycaemia associated with severe head injury, cerebral thrombosis, encephalitis or heat stroke and for rare congenital metabolic glycogen storage disease associated with hyperglycaemia.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B05-A01A; B05-A01B; B10-J02; B14-F09; B14-S04

L64 ANSWER 38 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:798749 HCAPLUS
DN 128:111006
TI Effect of obesity on the response to insulin therapy in noninsulin-dependent **diabetes** mellitus
AU Yki-Jarvinen, Hannele; Ryysy, Leena; Kauppila, Marjut; Kujansuu, Eila; Lahti, Jorma; Marjanen, Tapani; Niskanen, Leo; Rajala, Sulo; Salo, Seppo; Seppala, Pentti; Tulokas, Timo; Viikari, Jorma; Taskinen, Marja-Riitta
CS Department of Medicine, Division of Endocrinology and Diabetology, University of Helsinki, Helsinki, FIN-00290, Finland
SO J. Clin. Endocrinol. Metab. (1997), 82(12), 4037-4043

CODEN: JCEMAZ; ISSN: 0021-972X
PB Endocrine Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB An initial improvement in glycemic control is often followed by gradual deterioration of glycemia during insulin treatment of patients with noninsulin-dependent **diabetes** mellitus (NIDDM). The causes of such worsening were examd. in a 12-mo follow-up anal. of 100 insulin-treated NIDDM patients who received either **combination** therapy with insulin or insulin alone. In the entire group, glycemic control averaged 9.7% at 0 mo and 8.0%, 8.0%, 8.2%, and 8.5% at 3, 6, 9, and 12 mo, resp. Glycemic control at 12 mo was significantly worse than that at 3, 6, and 9 mo. Basal body mass index was the most significant predictor of deterioration in glycemic control. During 1 yr, HbA1c decreased almost 3-fold more in patients whose basal wt. was below the mean basal body mass index of 28.1 kg/m2 (nonobese patients) than in those whose wt. exceeded 28.1 kg/m2 (obese patients). Glycemic control improved similarly over 1 yr in the nonobese subjects and deteriorated similarly in the obese patients regardless of their treatment regimen. Insulin doses, per body wt., were similar in the nonobese and obese patients. The nonobese patients consistently gained less wt. during 12 mo of **combination** therapy with insulin than during insulin therapy alone. The treatment regimen did not influence wt. gain m the obese group. The following conclusions were reached: (1) after an initial good response, glycemic control deteriorates more in obese than in nonobese patients with NIDDM; (2) in obese patients, wt. gain per se cannot explain the poor glycemic response to **combination** or insulin therapy, but it may induce a disproportionately large increase in insulin requirements because of greater insulin resistance in the obese than in the nonobese; (3) in nonobese patients, glycemic control improves equally during 1 yr with **combination** therapy with insulin and insulin alone, but **combination** therapy with insulin is assocd. with less wt. gain than treatment with insulin alone, (4) wt. gain appears harmful, as it is assocd. with increases in blood pressure and low-d. lipoprotein cholesterol.
ST insulin therapy **diabetes** obesity
IT Non-insulin-dependent **diabetes** mellitus
(obesity effect on the response to insulin therapy in humans with)
IT Antidiabetic agents
(obesity effect on the response to insulin therapy plus antidiabetics in humans with noninsulin-dependent **diabetes**)
IT Obesity
(response to insulin therapy in humans with noninsulin-dependent **diabetes** and)
IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(obesity effect on the response to insulin therapy in humans with noninsulin-dependent **diabetes**)
IT **657-24-9**, Metformin **10238-21-8**, Glibenclamide
29094-61-9, Glipizide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(obesity effect on the response to insulin therapy in humans with noninsulin-dependent **diabetes** and receiving)

L64 ANSWER 39 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:212455 HCAPLUS
DN 126:287899
TI Evaluation of BTS 67 582, a novel antidiabetic agent, in normal and diabetic rats
AU Jones, R.B.; Dickinson, K.; Anthony, D.M.; Marita, A.R.; Kaul, C.L.; Buckett, W.R.

CS Knoll Pharmaceuticals, Research and Development, Nottingham, NG1 1GF, UK
SO Br. J. Pharmacol. (1997), 120(6), 1135-1143
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The effect of BTS 67 582, a novel antidiabetic agent, has been evaluated on plasma glucose and plasma insulin in normal and streptozotocin-induced diabetic rats. BTS 67 582 (3 to 300 mg kg-1, p.o.) caused a **dose** - and time- dependent **redn.** in plasma glucose and an increase in plasma insulin in both fasted and glucose-loaded normal rats. The ED50 for the glucose lowering effect of BTS 67 582 in fasted rats was 37.6, 18.4 and 18.5 mg kg-1 at 1, 2 and 4 h after administration resp. In streptozotocin-induced (50 mg kg-1, i.v.) diabetic rats, BTS 67 582 (37-147 mg kg-1, p.o.) caused significant redns. of plasma glucose following a glucose load, whereas glibenclamide (100 mg kg-1, p.o.) was ineffective. BTS 67 582 significantly increased plasma insulin compared to controls whereas glibenclamide did not. BTS 67 582 did not displace [3H]-glibenclamide from its binding sites in rat brain, guinea-pig ventricle or the HIT-T15 insulinoma .beta.-cell line. BTS 67 582 does not therefore appear to modulate its action via an effect on the "sulfonylurea" receptor. In fasted rats, the glucose lowering effect of BTS 67 582 (100 mg kg-1 p.o.) and glibenclamide (1 mg kg-1, p.o.) were antagonized by diazoxide (30 mg kg-1, i.p.). In addn. BTS 67 582, like glibenclamide, caused a dose-dependent rightward shift of cromakalim-induced relaxation of noradrenaline precontracted rat aortic strips, suggesting the involvement of KATP channels. In summary, BTS 67 582 produces a blood glucose-lowering effect in normal and streptozotocin-induced diabetic rats assocd. with increased insulin concns. This effect appears to be due to a blockade of ATP-sensitive potassium channel activity via a different binding site to that of glibenclamide.
ST BTS 67 582 antidiabetic insulin glucose
IT Potassium channel
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(ATP-sensitive; evaluation of BTS 67 582 in normal and diabetic rats)
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
Potassium channel blockers
(evaluation of BTS 67 582 in normal and diabetic rats)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(evaluation of BTS 67 582 in normal and diabetic rats)
IT 64-77-7, Tolbutamide **10238-21-8**, Glibenclamide 161748-40-9, BTS 67582
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(evaluation of BTS 67 582 in normal and diabetic rats)
IT 50-99-7, D-Glucose, biological studies 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(evaluation of BTS 67 582 in normal and diabetic rats)

L64 ANSWER 40 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:293551 HCAPLUS
DN 126:324719
TI Metformin hydrochloride: an antihyperglycemic agent
AU Klepser, Teresa B.; Kelly, Michael W.
CS College of Pharmacy, The University of Iowa, Iowa City, IA, 52242, USA
SO Am. J. Health-Syst. Pharm. (1997), 54(8), 893-903
CODEN: AHSPEK; ISSN: 1079-2082
PB American Society of Health-System Pharmacists
DT Journal; General Review

LA English
CC 1-0 (Pharmacology)
AB A review with 58 refs. The pharmacol., pharmacokinetics, clin. efficacy, adverse effects, drug interactions, and **dosage** and administration of metformin hydrochloride are discussed. Metformin is an antihyperglycemic agent; it lowers the blood glucose concn. without causing hypoglycemia. Proposed mechanisms of action include decreased intestinal absorption of glucose, increased glucose uptake from the blood into the tissues, decreased glucose prodn. in the liver, and decreased insulin requirements for glucose disposal. Metformin is slowly absorbed from the small intestine and does not undergo hepatic metab. The half-life is about five hours. The major route of elimination is renal; the drug is contraindicated in patients with impaired renal function. In double-blind, placebo-controlled trials, metformin has shown efficacy in the treatment of non-insulin-dependent **diabetes** mellitus (NIDDM). The drug is as effective as sulfonylureas in patients with **diabetes** who are nonobese or obese and whose **diabetes** is uncontrolled by diet alone. Metformin may be useful as add-on **therapy** in obese patients with **diabetes** uncontrolled by sulfonylureas and diet. Lipid profiles may be favorably influenced. The most common adverse effects are gastro-intestinal. A rare but potentially fatal adverse effect is lactic acidosis. Metformin has the potential to interact with cationic drugs eliminated by the renal tubular pathway. The usual effective **dosage** is **1.5**-2.5 g/day orally in two or three divided **doses**. Metformin hydrochloride is an effective alternative to sulfonylureas in obese and non-obese patients with NIDDM in whom diet alone has not achieved glycemic control, and it may be useful as add-on **therapy** in patients whose **diabetes** has not responded adequately to sulfonylureas plus dietary measures.
ST review metformin hydrochloride antihyperglycemic pharmacol
IT Antidiabetic agents
(metformin hydrochloride: an antihyperglycemic agent)
IT **1115-70-4**, Metformin hydrochloride
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin hydrochloride: an antihyperglycemic agent)

L64 ANSWER 41 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 97172248 EMBASE
DN 1997172248
TI Combination of **low-dose** niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control.
AU Gardner S.F.; Marx M.A.; White L.M.; Granberry M.C.; Skelton D.R.; Fonseca V.A.
CS S.F. Gardner, Department of Pharmacy Practice, College of Pharmacy, Univ. of Arkansas for Med. Sciences, 4301 W. Markham St., Little Rock, AR 72205, United States. gardner@cop.uams.edu
SO Annals of Pharmacotherapy, (1997) 31/6 (677-682).
Refs: 22
ISSN: 1060-0280 CODEN: APHRER
CY United States
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English; French; Spanish
AB OBJECTIVES: To determine the efficacy and tolerability of the addition of **low dose** niacin (1.5 g/d) in a diabetic hypercholesterolemic population who were unable to attain desired lipid control with **low-dose** (20 mg) pravastatin monotherapy.

RESEARCH DESIGN AND METHODS: This was a prospective, open label study conducted over a 14 week period. Twenty-three diabetic patients with low-density lipoprotein (LDL) cholesterol concentrations of at least 150 mg/dL after dietary therapy were recruited from the outpatient diabetes clinic of a university teaching hospital. After 4 weeks of dietary stabilization and baseline determination of the lipid profile and glycemic control, patients received pravastatin 20 mg once daily for 4 weeks. Laboratory parameters were reassessed and niacin was added to the regimen in qualifying patients. Over 2 weeks patients' regimens were titrated to a maximal dosage of 500 mg tid. Patients continued to receive the combination regimen for 4 weeks and were reassessed. MEASUREMENTS AND MAIN RESULTS: Sixteen patients (14 non-insulin-dependent diabetes mellitus. 2 insulin- dependent diabetes mellitus) completed the study. Mean fasting blood sugar and fructosamine concentrations were unchanged throughout the study. Five patients required minor alterations (3 increased, 2 decreased) in their hypoglycemic regimens during the study. The addition of **low dose** niacin to pravastatin therapy resulted in a significant lowering of LDL cholesterol compared with pravastatin monotherapy. CONCLUSIONS: **Low-dose** niacin is a promising addition to hydroxymethylglutaryl-coenzyme A reductase inhibitor therapy in the treatment of hypercholesterolemia in patients with diabetes mellitus.

CT Medical Descriptors:
***diabetes mellitus: DT, drug therapy**
*hypercholesterolemia: DT, drug therapy
adult
aged
article
clinical article
clinical trial
controlled study
diabetes control
dose response
drug effect
female
human
insulin dependent diabetes mellitus: DT, drug therapy
male
non insulin dependent diabetes mellitus: DT, drug therapy
priority journal
Drug Descriptors:
*antidiabetic agent: DT, drug therapy
*fructosamine: EC, endogenous compound
*glucose: EC, endogenous compound
*lipid: EC, endogenous compound
*nicotinic acid: CT, clinical trial
*nicotinic acid: DT, drug therapy
*nicotinic acid: DO, drug dose
***nicotinic acid: CB, drug combination**
*pravastatin: DT, drug therapy
***pravastatin: CB, drug combination**
*pravastatin: CT, clinical trial
cholesterol: EC, endogenous compound
glibenclamide: DT, drug therapy
glipizide: DT, drug therapy
high density lipoprotein cholesterol: EC, endogenous compound
human insulin: DT, drug therapy
isophane insulin: DT, drug therapy
lipoprotein a: EC, endogenous compound
low density lipoprotein cholesterol: EC, endogenous compound
metformin: DT, drug therapy
triacylglycerol: EC, endogenous compound
RN (fructosamine) 4429-04-3; (glucose) 50-99-7, 84778-64-3; (lipid) 66455-18-3; (nicotinic acid) 54-86-4, 59-67-6; (pravastatin) 81131-74-0;

(cholesterol) 57-88-5; (glibenclamide) **10238-21-8**; (glipizide) 29094-61-9; (human insulin) 11061-68-0; (isophane insulin) 9004-17-5; (metformin) **1115-70-4, 657-24-9**

L64 ANSWER 42 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:39717 HCAPLUS
DN 128:162753
TI Efficacy of metformin in type II **diabetes**: results of a double-blind, placebo-controlled, **dose**-response trial
AU Garber, Alan J.; Duncan, Theodore G.; Goodman, Anita M.; Mills, Donna J.; Rohlf, Jane L.
CS Dep. Medicine, Baylor Coll. Med., Houston, TX, USA
SO Am. J. Med. (1997), 103(6), 491-497
CODEN: AJMEAZ; ISSN: 0002-9343
PB Excerpta Medica, Inc.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The purpose of this study was to evaluate the efficacy and safety of various **dosages** of metformin as compared with placebo in patients with type II **diabetes** mellitus. A 14-wk, multicenter, double-blind, **dose**-response study was conducted. After a 3-wk, single-blind, placebo-controlled washout, 451 patients with fasting plasma glucose levels of at least 180 mg/dL were randomized to receive an 11-wk course of placebo or metformin given at 500, 1000, 1500, 2000, or 2500 mg daily. Metformin improved glucose variables as compared with placebo. The adjusted mean changes in fasting plasma glucose from baseline assocd. with each metformin group at week 7, 11, or at endpoint exceeded those assocd. with placebo by 19 to 84 mg/dL at **dosages** of 500 to 2000 mg daily, resp. The corresponding between-group differences in glycated Hb (HbA1c) **ranged** from 0.5% to 2.0% at **dosages** of 500 to 2000 mg daily, resp. All between-group differences were significant ($P < 0.05$) for both fasting plasma glucose and HbA1c at week 7, week 11, and endpoint, except for the difference between placebo and metformin 500 mg in fasting plasma glucose at endpoint ($P = 0.054$). Treatment-related adverse events occurred in 15% of patients in the placebo group and in 28% in the metformin group ($P = 0.02$); these were primarily manifested as digestive disturbances, such as diarrhea. Metformin lowered fasting plasma glucose and HbA1c generally in a **dose**-related manner. Benefits were obsd. with as little as 500 mg of metformin; maximal benefits were obsd. at the upper limits of the recommended daily **dosage**. All **dosages** were well tolerated. Metformin appears to be a useful **therapeutic** option for physicians who wish to titrate drug **therapy** to achieve target glucose concns.
ST metformin type II **diabetes** mellitus
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(metformin efficacy in treatment of humans with NIDDM)
IT **657-24-9**, Metformin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin efficacy in treatment of humans with NIDDM)

L64 ANSWER 43 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:272662 HCAPLUS
DN 126:324774
TI Metformin and insulin: is there a role for combination **therapy**?
AU Daniel, Jacqueline R.; Hagmeyer, Kathleen O.
CS Department of Pharmacy, Summa Health System, Akron, OH, 44309, USA
SO Ann. Pharmacother. (1997), 31(4), 474-480
CODEN: APHRER; ISSN: 1060-0280
PB Harvey Whitney Books Co.
DT Journal; General Review

LA English
CC 1-0 (Pharmacology)
AB A review with .apprx.19 refs. The purpose of this study is to review the literature on concomitant insulin and metformin **therapy** in patients with type 1 **diabetes** to det. the potential for combination **therapy**. A MEDLINE and bibliog. search (1966-1996) of the literature pertaining to metformin and phenformin and their combined use with insulin in the treatment of patients with type 1 **diabetes** mellitus was performed. All human studies using metformin with insulin were included in the anal. Studies using phenformin with insulin were also included due to its similarities to metformin. The recent availability of metformin provides some new options for treating **diabetes** mellitus. One possibility is the use of this medication in conjunction with insulin in patients with type 1 **diabetes**. Although this seems like a potentially beneficial combination, there is currently no recommendation for use in this manner. Experience with combination metformin and insulin **therapy** has consistently demonstrated a redn. in insulin requirements. Studies have not been of necessary size or duration to definitively prove the benefits of this insulin **dose redn.** or any other benefits of combination **therapy**. When metformin is added to insulin **therapy**, insulin requirements are likely to decrease. Although one would anticipate benefits from redn. in circulating insulin concns., the studies do not provide data to det. if benefits of combination **therapy** outweigh risks. Further studies of larger size and longer duration are needed before the use of metformin with insulin can be routinely recommended in patients with type 1 **diabetes**.
ST review metformin insulin **diabetes** phenformin antidiabetic
IT Antidiabetic agents
Insulin-dependent **diabetes** mellitus
(metformin and insulin may have a role for combination **therapy** in humans)
IT 114-86-3, Phenformin **657-24-9**, Metformin 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin and insulin may have a role for combination **therapy** in humans)

L64 ANSWER 44 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:548993 HCAPLUS
DN 127:199538
TI Metformin and its role in the management of type-2-**diabetes**
AU Haupt, Ekke; Panten, Uwe
CS Zentrum Nervenheilkunde, Universitat Rostock, Rostock, Germany
SO Med. Klin. (Munich) (1997), 92(8), 472-479,505
CODEN: MEKLA7; ISSN: 0723-5003
PB Urban & Vogel
DT Journal; General Review
LA German
CC 1-0 (Pharmacology)
AB A review with 73 refs. is given on effects, pharmacokinetics, and clin. studies of metformin in type-2 diabetic patients. Metformin lowers fasting blood glucose levels by 17-37%, postprandial blood glucose by up to 44.5% and HbA1c by 0.8-3.1%. Metformin reduces raised plasma insulin levels in cases of metabolic syndrome by 30% and reduces the insulin requirement of type-2 insulin-treated diabetics by 15-32%. It has well documented effects on various rheol. parameters. In overweight type-2 diabetics, metformin shows the same level of hypoglycemic effects as all of the important sulfonylurea derivs. used in Europe. Biguanides, similarly to wt. redn., lead to a redn. of hyperinsulinemia, which is by contrast exacerbated by sulfonylureas and exogenous insulin. The risk of lactic acidosis can probably eliminated entirely if **dosage** instructions and contraindications are obsd. carefully. The cause of such

neglect in 83% of all cases was limited on renal function (serum creatinine >**1.5** mg%). Regarding morbidity and mortality from lactic acidosis, metformin **therapy** is no riskier than treatment with the sulfonylurea deriv. glibenclamide, taking into account the incidence of fatal hypoglycemias with the latter.

ST review metformin **diabetes**

IT Non-insulin-dependent **diabetes** mellitus
(metformin for **therapy** of **diabetes** type 2)

IT **657-24-9**, Metformin
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(for **therapy** of **diabetes** type 2)

L64 ANSWER 45 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:555879 HCAPLUS
DN 127:214970
TI Pioglitazone and metformin reverse insulin resistance induced by tumor necrosis factor-alpha in liver cells
AU Solomon, Solomon S.; Mishra, S. K.; Cwik, C.; Rajanna, B.; Postlethwaite, A. E.
CS Research Medical Services, VAMC, Memphis, TN, 38104, USA
SO Horm. Metab. Res. (1997), 29(8), 379-382
CODEN: HMMRA2; ISSN: 0018-5043
PB Thieme
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Tumor necrosis factor-.alpha. (TNF-.alpha.) was recently implicated as a cause of insulin resistance (IR) in obesity and non-insulin dependent **diabetes** mellitus (NIDDM). To examine mechanisms involved, IR was induced in H-411 E cells with graded **doses** of TNF-.alpha. and measured the ability of insulin (INS) to stimulate both calmodulin (CaM) mRNA and glucose utilization. With TNF-.alpha. concn. at 1 ng/mL and 104 .mu.U/mL INS, metformin 10 .mu.M, and pioglitazone **1.5** .mu.M, reversed the IR induced by TNF-.alpha. restoring biol. response to 100% of INS effect alone. Furthermore, comparable results were obtained with glucose utilization/oxidn. expts. in the H-411E cells using glucose U-14C, trapping 14CO2 release in a hyamine filter and extg. 14C labeled lipids with Dole's reagent. In conclusion, these data add scientific support for the use of both metformin and pioglitazone in treatment of IR in NIDDM patients and support a rationale for use of these drugs alone, and in conjunction with oral agents and/or INS treatment.

ST pioglitazone metformin insulin calmodulin TNFalpha **diabetes**

IT Calmodulins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect of pioglitazone and metformin on calmodulin gene expression in liver cells)

IT Non-insulin-dependent **diabetes** mellitus
(pioglitazone and metformin reverse insulin resistance induced by TNF-.alpha. in liver cells)

IT Tumor necrosis factor .alpha.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(pioglitazone and metformin reverse insulin resistance induced by TNF-.alpha. in liver cells)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(pioglitazone and metformin reverse insulin resistance induced by TNF-.alpha. in liver cells)

IT **657-24-9**, Metformin 111025-46-8, Pioglitazone
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pioglitazone and metformin reverse insulin resistance induced by

TNF-.alpha. in liver cells)

L64 ANSWER 46 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:185495 HCAPLUS
DN 126:258925
TI Antidiabetic effects of pioglitazone.cntdot.HCl alone or in combination with insulin or sulfonylurea in diabetic animals
AU Odaka, Hiroyuki; Kataoka, Osamu; Suwa, Yoko; Tayuki, Noriko; Amano, Nobuyuki; Ikeda, Hitoshi
CS Pharmaceutical Res. Lab. II, Takeda Chem. Industries Ltd., Japan
SO Yakuri to Chiryo (1997), 25(2), 345-353
CODEN: YACHDS; ISSN: 0386-3603
PB Raifu Saiensu Shuppan K.K.
DT Journal
LA Japanese
CC 1-10 (Pharmacology)
AB The antidiabetic effects of pioglitazone.cntdot.HCl alone or in combination with insulin or sulfonylurea were investigated in diabetic animals. Seventeen-week-old GK rats, a model of nonobese noninsulin-dependent **diabetes**, showed mild hyperglycemia and their plasma glucose did not decrease by the oral administration of pioglitazone.cntdot.HCl (10 mg/kg/day) for 7 days. To exaggerate hyperglycemia (>400 mg/dL), GK rats were given a 30% sucrose soln. in addn. to the stock diet and water from 12 wk of age. They were orally administered with pioglitazone.cntdot.HCl (3 mg/kg/day) and/or i.p. injected with insulin (2,4 and 1U/rat, b.i.d. for 1st, 2nd and the last 2 wk, resp.) for 4 wk. Control GK rats drinking a sucrose soln. showed severe diabetic symptoms such as glucosuria (>7 g/day) and hypertriglyceridemia (>250 mg/dL). Pioglitazone.cntdot.HCl reduced plasma glucose, glycated Hb and urinary glucose to 71, 94 and 72% of control, resp. Insulin at a **dose** of 1U/rat **reduced** plasma glucose, glycated Hb and urinary glucose of the levels of 61, 90 and 24% of control. Higher dose of insulin showed the similar effect. On the other hand, pioglitazone.cntdot.HCl in combination with insulin showed marked hypoglycemic and hypolipidemic effects; urinary glucose disappeared and plasma triglyceride and cholesterol decreased to 22 and 80% of control. Six-week-old, male SD rats were i.v. injected with streptozotocin (STZ) at a dose of 60 mg/kg to render diabetic. They are insulin-dependent **diabetes** (IDDM). From week 1, they were orally administered with pioglitazone.cntdot.HCl (10 mg/kg/day) and i.p. injected with insulin (6,8 or 10U/rat/day) for 1 wk. However no marked decrease in plasma and urinary glucose were obsd. Therefore, insulin (4,6 or 8U/rat) were injected b.i.d. together with an oral administration with pioglitazone.cntdot.HCl (10 mg/kg/day) for further 1 wk. Control STZ-diabetic rats showed hyperglycemia and glucosuria; plasma glucose and urinary glucose levels were 584 mg/dL and 13.3 g/day, resp. Although pioglitazone.cntdot.HCl (10 mg/kg/day) did not reduce these diabetic symptoms, insulin (4,6 and 8U/rat, b.i.d.) **dose**-dependently **reduced** plasma glucose to 87, 83 and 75% of control and decreased urinary glucose to 74,49 and 44% of control. Pioglitazone.cntdot.HCl in combination with insulin showed much more potent hypoglycemic effect than insulin alone; pioglitazone.cntdot.HCl with 4,6 and 8U/rat, b.i.d. of insulin decreased urinary glucose to 32,49 and 26% of control, resp. Fourteen-week-old, male Wistar fatty rats, a model of obese noninsulin-dependent **diabetes**, were orally administered with pioglitazone.cntdot.HCl (3 mg/kg/day) for 7 days, fasted for 20 h, and then oral glucose tolerance test was performed with or without glibenclamide (3 mg/kg). Pioglitazone.cntdot.HCl reduced both glucose-induced insulin secretion and delta glucose area to 45% and 47% of control, resp. On the other hand, a single administration of glibenclamide enhanced the glucose-induced insulin secretion but did not result in a significant change in delta glucose area. Pioglitazone.cntdot.HCl in combination with glibenclamide reduced insulin secretion slightly, but delta glucose area markedly to 21% of control.

These results indicate that pioglitazone may be a useful adjunct to insulin **therapy** in the treatment of both IDDM and NIDDM, and to sulfonylurea **therapy** in NIDDM.

ST antidiabetic pioglitazone insulin sulfonylurea

IT Antidiabetic agents
(antidiabetic effects of pioglitazone alone or in combination with insulin or sulfonylurea)

IT 9004-10-8, Insulin, biological studies **10238-21-8**, Glibenclamide 111025-46-8, Pioglitazone
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antidiabetic effects of pioglitazone alone or in combination with insulin or sulfonylurea)

L64 ANSWER 47 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:196703 HCAPLUS
DN 126:258797
TI Eprosartan, an angiotensin II receptor antagonist, does not affect the pharmacodynamics of glyburide in patients with type II **diabetes** mellitus
AU Martin, David E.; DeCherney, Stephen; Ilson, Bernard E.; Jones, Beverly A.; Boike, Steven C.; Freed, Martin I.; Jorkasky, Diane K.
CS SmithKline Beecham Clinical Pharmacology Unit, Univ. Pennsylvania Health System, Philadelphia, PA, USA
SO J. Clin. Pharmacol. (1997), 37(2), 155-159
CODEN: JCPCBR; ISSN: 0091-2700
PB Lippincott-Raven
DT Journal
LA English
CC 1-8 (Pharmacology)
AB The potential for Eprosartan, a nonbiphenyl tetrazole angiotensin II receptor antagonist, to affect the 24-h plasma glucose profiles in type II diabetic patients treated with glyburide was investigated in this randomized, placebo-controlled, double-blind (Eprosartan-placebo phase only), two-period, period-balanced, crossover study. All patients received a stable oral **dose** (3.75-10 mg/day) of glyburide for at least 30 days before the first **dose** of double-blind study medication was administered. Patients were randomized to receive either 200-mg oral **doses** of Eprosartan twice daily or matching oral placebo **doses** concomitantly with glyburide for 7 days during each treatment period. After a min. washout period of 14 days, patients were crossed over to the alternate treatment. Serial samples to measure glucose concns. in plasma were collected over a 24-h period on the day before administration of Eprosartan or placebo and again on day 7. Mean glucose concns. were comparable between treatment groups before administration of Eprosartan or placebo. The point est. (90% confidence interval) for the **ratio** of the av. mean 24-h plasma glucose concns. of Eprosartan + glyburide to placebo + glyburide after 7 days of administration was 0.96 (0.90, 1.01). Eprosartan did not significantly alter the 24-h plasma glucose profile in patients with type II **diabetes** mellitus who were previously stabilized on glyburide.

ST eprosartan angiotensin receptor antagonist glyburide; glyburide **diabetes** mellitus

IT Angiotensin II receptor antagonists
Non-insulin-dependent **diabetes** mellitus
(eprosartan, angiotensin II receptor antagonist, does not affect pharmacodynamics of glyburide in human patients with type II **diabetes** mellitus)

IT **10238-21-8**, Glyburide 133040-01-4, Eprosartan
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(eprosartan, angiotensin II receptor antagonist, does not affect pharmacodynamics of glyburide in human patients with type II **diabetes** mellitus)

L64 ANSWER 48 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:742043 HCAPLUS
DN 128:57087
TI Concomitant administration of the .alpha.-glucosidase inhibitor voglibose (AO-128) does not alter the pharmacokinetics of glibenclamide
AU Kleist, P.; Ehrlich, A.; Suzuki, Y.; Timmer, W.; Wetzelsberger, N.; Lucker, P. W.; Fuder, H.
CS Takeda Euro R&D Centre GmbH, Frankfurt/Main, D-60486, Germany
SO Eur. J. Clin. Pharmacol. (1997), 53(2), 149-152
CODEN: EJCPAS; ISSN: 0031-6970
PB Springer
DT Journal
LA English
CC 1-4 (Pharmacology)
AB Voglibose is a new and potent inhibitor of .alpha.-glucosidases used for treatment of **diabetes** mellitus. It increases gastro-intestinal motility and could thus affect absorption of other concurrently administered antidiabetic drugs. The aim of this study was to investigate whether or not voglibose modifies the pharmacokinetics of glibenclamide, a widely used oral antidiabetic, and the glibenclamide-induced decrease in fasting serum glucose. Twelve healthy male subjects were included in this double-blind cross-over study and received a single 1.75-mg **dose** of glibenclamide on the 8th day of continuous administration of either placebo (ref.) or voglibose 5 mg t.i.d. (test). Blood samples were taken to det. the pharmacokinetic characteristics of glibenclamide and the test/ref. ratios were evaluated according to bioequivalence criteria. Addnl. blood samples were taken to measure serum glucose on the same day. The concn.-time course of glibenclamide under concomitant voglibose administration was similar to that under placebo. The equivalence **ratio** (test/ref.) for the pharmacokinetic characteristics AUCnorm was 1.03 (geometric mean; 0.95-1.11, 90% confidence interval) an dCmax,norm1.01(0.94-1.08). The parameters were within the accepted **range** of 0.8-1.25(AUC) or 0.7-1.43 (Cmax), thus fulfilling equivalence criteria and indicting no effect of voglibose on glibenclamide kinetics. The glibenclamide-induced decrease in fasting serum glucose concn. was similarly independent of placebo or voglibose co-administration. Voglibose did not interact with glibenclamide on a pharmacokinetic level. Concomitant treatment was well tolerated and has been proven to be safe for further clin. use.
ST antidiabetic voglibose glibenclamide pharmacokinetic interaction
IT Antidiabetic agents
Pharmacokinetic drug interactions
(.alpha.-glucosidase inhibitor voglibose (AO-128) does not alter glibenclamide pharmacokinetics)
IT 83480-29-9, Voglibose
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.alpha.-glucosidase inhibitor voglibose (AO-128) does not alter glibenclamide pharmacokinetics)
IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.-glucosidase inhibitor voglibose (AO-128) does not alter glibenclamide pharmacokinetics)
IT **10238-21-8**, Glibenclamide
RL: BPR (Biological process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(.alpha.-glucosidase inhibitor voglibose (AO-128) does not alter glibenclamide pharmacokinetics)

L64 ANSWER 49 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:82962 HCAPLUS
DN 126:181167
TI Hypoglycemic and insulinotropic effects of a novel oral antidiabetic

agent, (-)-N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166)
AU Ikenoue, Takao; Akiyoshi, Megumi; Fujitani, Shoji; Okazaki, Kyoko; Kondo, Nobuo; Maki, Toshio
CS Life Science Laboratories, Central Research Laboratories, Ajinomoto Co., Inc., Yokohama, 244, Japan
SO Br. J. Pharmacol. (1997), 120(1), 137-145
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
CC 1-10 (Pharmacology)
AB (-)-N-(trans-4-isopropylcyclohexanecarbonyl)D-phenylalanine (A-4166), a novel oral hypoglycemic agent is a non-sulfonylurea insulin secretagogue. We investigated the insulin-releasing action and hypoglycemic effect of A-4166 compared to sulfonylureas in vitro and in vivo. A-4166 stimulated insulin secretion from rat freshly isolated pancreatic islets at concns. from 3 .times. 10-6 M to 3 .times. 10-4 M in the presence of 2.8 mM glucose. There was no obvious difference in glucose dependency between the insulinotropic effect of A-4166 and that of glibenclamide, and no additive or synergistic effect was obsd. between these two drugs. A-4166 displaced [3H]-glibenclamide bound to intact HIT-T15 cells in a concn.-dependent manner. The Ki value was 4.34 .+-. 0.04 .times. 10-7 M, and the displacement potency of A-4166 was between that of glibenclamide and tolbutamide, being similar to that of gliclazide. In fasted beagle dogs, A-4166 showed a **dose**-dependent hypoglycemic effect after oral administration over the **range** 1 to 10 mg kg-1. The hypoglycemic action of A-4166 showed an earlier onset and a shorter duration than that of sulfonylureas. Simultaneous measurement of plasma insulin levels revealed that the hypoglycemic effect of A-4166 was caused by a rapid-onset and brief burst of insulin secretion. The pharmacokinetic profile of A-4166 was consistent with the changes of the blood glucose and plasma insulin levels. Although the in vitro insulin-releasing effect of A-4166 was similar to that of sulfonylureas, its hypoglycemic effect was more rapid and shorter-lasting, assocd. with rapid absorption and clearance. Thus, A-4166 may be useful in suppressing postprandial hyperglycemia in patients with non-insulin-dependent **diabetes** mellitus.
ST hypoglycemic insulinotropic antidiabetic phenylalanine deriv A4166
IT Antidiabetic agents
(hypoglycemic and insulinotropic effects of A-4166)
IT 105816-04-4, A-4166
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(hypoglycemic and insulinotropic effects of A-4166)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(hypoglycemic and insulinotropic effects of A-4166)
IT 64-77-7, Tolbutamide **10238-21-8**, Glibenclamide 21187-98-4, Gliclazide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hypoglycemic and insulinotropic effects of A-4166 compared to sulfonylureas)

L64 ANSWER 50 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:539877 HCAPLUS
DN 127:229475
TI Metformin, plasma glucose and free fatty acids in type II diabetic out-patients: results of a clinical study
AU Gregorio, F.; Ambrosi, F.; Manfrini, S.; Santucci, A.; Filipponi, P.
CS Metabolic Unit, Department of Internal Medicine, University of Perugia and Anti-Diabetic Unit, E. Profili' General Hospital, Fabriano (AN), 60044,

Italy
SO Diabetes Res. Clin. Pract. (1997), 37(1), 21-33
CODEN: DRCPE9; ISSN: 0168-8227
PB Elsevier
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Abnormalities in free fatty acid (FFA) metab. are an intrinsic feature of type II **diabetes** mellitus and may even play a role in the development of glycemic imbalance. This study investigated whether the anti-diabetic drug metformin can reduce FFA levels in clin. practice and whether this correlates with its anti-diabetic effect. For 6 mo metformin was added to sulfonylurea **therapy** in 68 type II diabetic outpatients with poor glycemic control, being administered before meals and at bed-time. Basal and daily area-under-the-curve (AUC) glucose levels dropped (both P<0.0005) like basal and daily AUC FFA levels (P<0.004 and P<0.001 resp.) redns. were all correlated (P<0.001 and P<0.003 resp.). Redns. in fasting and daily AUC glucose correlated more closely with body fat distribution, expressed by waist-hip **ratio** (WHR) (P<0.006 and P<0.004 resp.), than with the body mass index (BMI) (P<0.02 and P<0.04 resp.). Similarly fasting and daily AUC FFA correlated with WHR (P<0.007 and P<0.01 resp.) but not with BMI (both P = ns). Subdividing male and female diabetic patients into groups with low and high WHRs, fasting and daily AUC glucose were reduced in men (P<0.01 and P<0.02) and in women (P<0.02 and P<0.04 resp.) with low WHRs less than in men and in women with higher WHRs (for each gender P<0.0001 and P<0.0002 resp.). Decreases in fasting and daily AUC FFA, which did not reach significance in either men or women with low WHRs, were statistically significant in men (P<0.03 and P<0.01 resp.) and in women (P<0.02 and P<0.005 resp.) with high WHRs. These findings suggest that an improvement in FFA plasma levels might contribute to metformin's anti-diabetic activity which appears to be more marked in patients with high WHRs. Moreover adding a bed-time **dosage** to the std. administration at meal times seems to be an effective **therapeutical** strategy.
ST metformin fatty acid type II **diabetes**; antidiabetic metformin noninsulin dependent **diabetes** mellitus
IT Fatty acids, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of; metformin, plasma glucose and free fatty acids in type II diabetic out-patients)
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(metformin, plasma glucose and free fatty acids in type II diabetic out-patients)
IT 50-99-7, Glucose, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(metformin, plasma glucose and free fatty acids in type II diabetic out-patients)
IT **657-24-9**, Metformin
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin, plasma glucose and free fatty acids in type II diabetic out-patients)

L64 ANSWER 51 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 6
AN 1997:116496 HCAPLUS
DN 126:113182
TI Furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum
IN Inman, Wayne D.; King, Steven R.; Evans, Joseph L.; Luo, Jian
PA Shaman Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM C07D307-92
ICS A61K031-365
CC 1-10 (Pharmacology)
Section cross-reference(s): 30, **63**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9639401	A1	19961212	WO 1996-US8427	19960603
	W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5747527	A	19980505	US 1995-479049	19950606
	AU 9660316	A1	19961224	AU 1996-60316	19960603
PRAI	US 1995-479049	19950606			
	WO 1996-US8427	19960603			

AB Hypoglycemically active eremophilanolide sesquiterpenes which can be isolated from Psacalium spp., processes for obtaining the novel eremophilanolide sesquiterpenes, and methods for their use as hypoglycemic agents e.g. in the treatment of **diabetes**, are described. Further described is the use of epicacalone, cacalone, cacalol or dimaturin as hypoglycemic agents, for example, in the treatment of **diabetes**. In a preferred embodiment, the hypoglycemically active compds. are obtained from the roots of Psacalium decompositum. As agents for the treatment of **diabetes**, the hypoglycemically active compds. of the present inventions are useful for treating insulin-dependent (type I) and/or non-insulin-dependent (type-II) **diabetes**.

ST furanoeremophilane eremophilanolide sesquiterpene isolation antidiabetic hypoglycemic; Psacalium sesquiterpene isolation antidiabetic hypoglycemic

IT Sesquiterpenes
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(eremophilane; furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT Antidiabetic agents
Drug delivery systems
Psacalium
Psacalium decompositum
(furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT Sulfonylureas
.beta.3-Adrenoceptor agonists
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, isolation thereof from Psacalium decompositum, and **combinations** with other hypoglycemic agents)

IT Transport (biological)
(glucose; furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT Sesquiterpenes
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(naphthofuran; furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT 7439-89-6DP, Iron, complexes with furanoeremophilanes and eremophilanolide sesquiterpenes 7439-95-4DP, Magnesium, complexes with furanoeremophilanes and eremophilanolide sesquiterpenes 7440-66-6DP, Zinc, complexes with furanoeremophilanes and eremophilanolide sesquiterpenes 24393-79-1P, Cacalol 26294-92-8P, Cacalone 60428-00-4P, Epicacalone 186252-31-3P 186252-54-0P 186252-56-2P
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT 24393-79-1D, iron complexes 24393-79-1D, magnesium complexes 24393-79-1D, zinc complexes 26294-92-8D, iron complexes 26294-92-8D, magnesium complexes 26294-92-8D, zinc complexes 60428-00-4D, iron complexes 60428-00-4D, magnesium complexes 60428-00-4D, zinc complexes 186252-31-3D, iron complexes 186252-31-3D, magnesium complexes 186252-31-3D, zinc complexes 186252-32-4 186252-33-5 186252-34-6 186252-35-7 186252-36-8 186252-37-9 186252-38-0 186252-39-1 186252-40-4 186252-41-5 186252-42-6 186252-43-7 186252-44-8 186252-46-0 186252-48-2 186252-50-6 186317-61-3, Dimaturin calcium salt 186317-61-3D, iron complexes 186317-61-3D, magnesium complexes 186317-61-3D, zinc complexes
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide **657-24-9**, Metformin 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8, Insulin, biological studies **10238-21-8**, Glyburide 21187-98-4, Gliclazide 29094-61-9, Glipizide 56180-94-0, Acarbose 72432-03-2, Miglitol 97322-87-7, Troglitazone
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, isolation thereof from Psacalium decompositum, and **combinations** with other hypoglycemic agents)

IT 74315-95-0, .alpha.-Glycosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, isolation thereof from Psacalium decompositum, and **combinations** with other hypoglycemic agents)

IT 50-99-7, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(transport; furanoeremophilane and eremophilanolide sesquiterpenes for hypoglycemic agents and treatment of **diabetes**, and isolation thereof from Psacalium decompositum)

L64 ANSWER 52 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1996-200708 [20] WPIDS
CR 1996-200866 [20]
DNC C1996-063379
TI Use of extracts from Cryptolepis sp. contg. new and known quindoline alkaloid(s) - as hypoglycaemic agents for treating insulin dependent and non-insulin dependent diabetes, also reducing blood glucose levels in acute stress.
DC B02
IN BIERER, D E; BRUENING, R C; CARLSON, T J; FORT, D M; KING, S R; LUO, J

PA (SHAM-N) SHAMAN PHARM INC
CYC 65
PI WO 9609823 A1 19960404 (199620)* EN 61p A61K031-42
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU IS JP KG KP KR KZ LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TT UA UZ VN
AU 9537319 A 19960419 (199630) A61K031-42
US 5628999 A 19970513 (199725) 11p A61K035-78
US 5629319 A 19970513 (199725) 10p A61K031-44
US 5753790 A 19980519 (199827) C07D209-80
US 5917052 A 19990629 (199932) C07D209-80
ADT WO 9609823 A1 WO 1995-US12505 19950927; AU 9537319 A AU 1995-37319 19950927; US 5628999 A Div ex US 1994-314188 19940928, US 1995-470876 19950606; US 5629319 A Div ex US 1994-314188 19940928, US 1995-472036 19950606; US 5753790 A Div ex US 1994-314188 19940928, US 1995-472020 19950606; US 5917052 A US 1994-314188 19940928
FDT AU 9537319 A Based on WO 9609823
PRAI US 1994-314188 19940928; US 1995-470876 19950606; US 1995-472036 19950606; US 1995-472020 19950606
REP 2.Jnl.Ref
IC ICM A61K031-42; A61K031-44; A61K035-78; C07D209-80
ICS A61K031-40; C09B007-00
AB WO 9609823 A UPAB: 19960520
The use of an extract from a Cryptolepis sp. (obtd. as described in 'Preferred Process') or a quindoline alkaloid of formula (I) or a salt, as a hypoglycaemic agent, for reducing blood glucose levels or lowering triglyceride levels and treating diabetes mellitus, is new. (a) R1-R11 = H; (b) R1-R4 and R6-R11 = H; and R5 = Me; (c) R1-R4 and R6-R11 = H; R5 = Et, isopropyl, benzyl, Ph, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-iodophenyl, 2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4- dimethylaminophenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-pyridinyl, 2-, 3- or 4-imidazolyl, 2-, 3- or 4-hydroxybenzyl, 2-, 3- or 4-dimethylaminobenzyl, 2-, 3- or 4-methoxybenzyl, 2-, 3, or 4-chlorobenzyl, 2-, 3- or 4-bromobenzyl, 2-, 3- or 4-fluorobenzyl, 2-, 3- or 4-iodobenzyl, 2-, 3- or 4-pyridylmethyl, 2- or 4-imidazolylmethyl, cyclopropyl or isobutyl; (d) R1, R4, R6-R11 = H; R2, R3 = -CH2OCH2-; R5 = as defined for (c); (e) R1-R4, R6-R7 and R10-R11 = H; R8, R9 = -CH2O-CH2-; R5 = as defined for (c); (f) R1-R3, R6-R11 = H; R4, R5 = -CH2CH2-; (g) R1-R3, R6-R11 = H; R4, R5 = -CH2CH2CH2-; (h) R1-R4, R6-R11 = H; R5 = Me; 10a, 11 = dihydro; (i) R1-R4, R6-R11 = H; R5 = Me; 5a,5b = dihydro; (j) R1-R4, R6-R11 = H; R5 = Me; 5a, 5b, 10a, 11 = tetrahydro; (k) R1-R11 = H; 9a, 10 = dihydro; or (l) R1-R11 = H; and 10-methyl on N-10. (N.B. - R10 is not shown. Cpds. (IA), i.e. (I) but not definitions (a) (quindoline) or (cryptolepine), are new.
USE - The extracts and (I) can be used to reduce blood glucose levels in situations of acute stress, e.g. associated with hypothermia, trauma, sepsis, burns and general anaesthetics, and to treat hyperglycaemia associated with severe head injury, cerebral thrombosis, encephalitis or heat stroke; also rare congenital metabolic glycogen storage disease associated with hyperglycaemia. They can be used in the treatment of insulin-dependent (type I) and non-insulin dependent (type II) diabetes. They can be administered in conjunction with another hypoglycaemic agent, pref. a sulphonylurea (esp. acetohexamide, chlorpropamide, tolazamide tolbutamide, **glyburide**, glypizide or glyclazide), a biguanide (esp. **metformin** or buformin), a thiazolidinedione (esp. troglitazone), a beta3-adrenoceptor agonist, an alpha-glycoside inhibitor (esp. acarbose or miglatol) or insulin. (I) can also be used for research purposes, e.g. to investigate the mechanism and activity of hypoglycaemic agents.
Dwg.1/7
FS CPI
FA AB; GI; DCN
MC CPI: B06-D18; B14-F04; B14-F09; B14-J01B; B14-S04

L64 ANSWER 53 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 96226878 EMBASE
DN 1996226878
TI Metformin: A new oral biguanide.
AU Campbell R.K.; White J.R. Jr.; Saulie B.A.
CS College of Pharmacy, Washington State University,Pullman, WA, United States
SO Clinical Therapeutics, (1996) 18/3 (360-371).
ISSN: 0149-2918 CODEN: CLTHDG
CY United States
DT Journal; General Review
FS 003 Endocrinology
006 Internal Medicine
029 Clinical Biochemistry
036 Health Policy, Economics and Management
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions TitlesAdverse Reactions Titles
LA English
SL English
AB The biguanide metformin is an oral antihyperglycemic agent used in the treatment of patients with non-insulin-dependent diabetes mellitus (NIDDM). Metformin is an important addition to the drug therapy options available for these patients because it reduces blood glucose levels predominantly by decreasing hepatic glucose production and release and also by increasing peripheral tissue sensitivity to insulin; it does not stimulate insulin secretion from the beta cells in the pancreas. Metformin also has a potentially beneficial effect by reducing serum lipid levels. Its glycemic control is similar to that of the sulfonylureas and is effective as monotherapy or in combination with sulfonylureas or insulin. Unlike sulfonylureas and insulin, it does not cause a gain in body weight, and when used as monotherapy, it does not cause hypoglycemia. The most common side effects associated with metformin are mild, transient, gastrointestinal symptoms, which are usually self-limiting. These side effects can be minimized by initiating metformin therapy at a **low dose** and gradually titrating upward, and by taking metformin with meals. Lactic acidosis caused by metformin is rare, and the risk of this complication may be diminished by the observance of prescribing precautions and contraindications that avoid accumulation of metformin or lactate in the body. In patients who are not getting the desired effect with sulfonylureas, it is useful to combine sulfonylureas with metformin therapy. Metformin should be considered a first-line agent, particularly in obese and/or hyperlipidemic NIDDM patients.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
clinical article
drug cost
drug mechanism
gastrointestinal symptom: SI, side effect
glucose blood level
human
hyperlipidemia
insulin sensitivity
lactic acidosis: SI, side effect
lipid blood level
meal
obesity
oral drug administration
prescription
review
weight gain
Drug Descriptors:
*biguanide: DO, drug dose
*biguanide: PD, pharmacology

***biguanide: CB, drug combination**
*biguanide: CM, drug comparison
*biguanide: AE, adverse drug reaction
*biguanide: IT, drug interaction
*biguanide: PK, pharmacokinetics
*biguanide: DT, drug therapy
*metformin: AE, adverse drug reaction
*metformin: PD, pharmacology
*metformin: PK, pharmacokinetics
*metformin: DT, drug therapy
*metformin: DO, drug dose
*metformin: IT, drug interaction
*metformin: CM, drug comparison
***metformin: CB, drug combination**
chlorpropamide: CM, drug comparison
cimetidine: IT, drug interaction
glibenclamide: CB, drug combination
glibenclamide: DT, drug therapy
glipizide: CM, drug comparison
glucose: EC, endogenous compound
guar gum: IT, drug interaction
insulin: CB, drug combination
insulin: CM, drug comparison
insulin: DT, drug therapy
lipid: EC, endogenous compound
new drug: IT, drug interaction
new drug: DO, drug dose
new drug: AE, adverse drug reaction
new drug: PD, pharmacology
new drug: PK, pharmacokinetics
new drug: CM, drug comparison
new drug: CB, drug combination
new drug: DT, drug therapy
oral antidiabetic agent: DT, drug therapy
oral antidiabetic agent: AE, adverse drug reaction
oral antidiabetic agent: PD, pharmacology
oral antidiabetic agent: PK, pharmacokinetics
oral antidiabetic agent: IT, drug interaction
oral antidiabetic agent: DO, drug dose
oral antidiabetic agent: CM, drug comparison
oral antidiabetic agent: CB, drug combination
sulfonylurea derivative: CB, drug combination
sulfonylurea derivative: CM, drug comparison
sulfonylurea derivative: DT, drug therapy
RN (biguanide) 56-03-1; (metformin) **1115-70-4, 657-24-9;** (chlorpropamide) 94-20-2; (cimetidine) 51481-61-9, 70059-30-2; (glibenclamide) **10238-21-8;** (glipizide) 29094-61-9; (glucose) 50-99-7, 84778-64-3; (guar gum) 9000-30-0; (insulin) 9004-10-8; (lipid) 66455-18-3

L64 ANSWER 54 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:383352 HCAPLUS
DN 125:48139
TI Clinical pharmacokinetics of metformin
AU Scheen, Andre J.
CS Department Medicine, CHU Sart Tilman, Liege, Belg.
SO Clin. Pharmacokinet. (1996), 30(5), 359-371
CODEN: CPKNDH; ISSN: 0312-5963
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with .apprx.74 refs. The biguanide metformin (dimethylbiguanide) is an oral antihyperglycemic agent widely used in the management of non-insulin-dependent **diabetes** mellitus (NIDDM). Considerable

renewal of interest in this drug has been obsd. in recent years. Metformin can be detd. in biol. fluids by various methods, mainly using high performance liq. chromatog., which allows pharmacokinetic studies in healthy volunteers and diabetic patients. Metformin disposition is apparently unaffected by the presence of **diabetes** and only slightly affected by the use of different oral formulations. Metformin has an abs. oral bioavailability of 40 to 60%, and gastrointestinal absorption is apparently complete within 6 h of ingestion. An inverse relationship was obsd. between the **dose** ingested and the relative absorption with **therapeutic doses** **ranging** from 0.5 to 1.5g, suggesting the involvement of an active, saturable absorption process. Metformin is rapidly distributed following absorption and does not bind to plasma proteins. No metabolites or conjugates of metformin have been identified. The absence of liver metab. clearly differentiates the pharmacokinetics of metformin from that of other biguanides, such as phenformin. Metformin undergoes renal excretion and has a mean plasma elimination half-life after oral administration of between 4.0 and 8.7 h. This elimination is prolonged in patients with renal impairment and correlates with creatinine clearance. There are only scarce data on the relationship between plasma metformin concns. and metabolic effects. **Therapeutic** levels may be 0.5 to 1.0 mg/L in the fasting state and 1 to 2 mg/L after a meal, but monitoring has little clin. value except when lactic acidosis is suspected or present. Indeed, when lactic acidosis occurs in metformin-treated patients, early detn. of the metformin plasma concn. appears to be the best criterion for assessing the involvement of the drug in this acute condition. After confirmation of the diagnosis, treatment should rapidly involve forced diuresis or hemodialysis, both of which favor rapid elimination of the drug. Although serious, lactic acidosis due to metformin is rare and may be minimized by strict adherence to prescribing guidelines and contraindications, particularly the presence of renal failure. Finally, only very few drug interactions have been described with metformin in healthy volunteers. Plasma levels may be reduced by guar gum and .alpha.-glucosidase inhibitors and increased by cimetidine, but no data are yet available in the diabetic population.

ST review metformin pharmacokinetic

IT Pharmacokinetics
(clin. pharmacokinetics of metformin in humans)

IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(clin. pharmacokinetics of metformin in humans)

L64 ANSWER 55 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:468349 HCAPLUS
DN 125:132400
TI Metformin treatment in elderly type II diabetic patients
AU Gregorio, F.; Manfrini, S.; Testa, I.; Filipponi, P.
CS Metabolic Unit, Univ. Perugia, Perugia, I-06122, Italy
SO Arch. Gerontol. Geriatr., Suppl. (1996), 5(Elderly Patient), 261-270
CODEN: AGGSEU; ISSN: 0924-7947
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Pharmacol. treatment in elderly patients with type II, non-insulin dependent **diabetes** mellitus (NIDDM) is becoming a growing and complex problem in the clin. practice, since longevity in almost every population is increasing, and the prevalence of NIDDM also rises with age. It is generally indicated that age over 65-70 yr represents a specific contraindication against the administration of the biguanides since the risk of the drug-assocd. lactic acidosis increases with age. However very few data exist in literature about the effect of biguanides, particularly metformin, in aging patients. Therefore, we aimed to evaluate the effects of adding metformin to poorly controlled sulfonylurea-treated elderly

diabetic subjects for a one year period. Eighty-four type II diabetic patients aged more than 70 yr and with a poor glycemic control were recruited after an informed consent. All diabetic patients were treated with various sulfonylureas at medium **doses** and presented renal and liver biochem. function tests within normal **ranges** and were free of severe microangiopathy and respiratory or congestive heart failure. Metformin treatment was added to the previous sulfonylurea **dosages** in order to achieve a satisfactory glycemic control. All patients showed a marked improvement in the glycemic control with no significant modification in fasting blood lactate and a mild increase in the post-prandial lactate peak which, however, always felt largely within the normal **ranges**. Metformin also improved some metabolic vascular risk factors such as plasma cholesterol levels that were reduced, circulating HDL-cholesterol levels that mildly but significantly increased and uric acid that was lowered. In conclusion our data further support the opinion that metformin has not to be denied to diabetic patients on the sole basis of they age.

ST metformin hypoglycemic **diabetes**

IT Antidiabetics and Hypoglycemics
(metformin treatment in elderly type II diabetic humans)

IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin treatment in elderly type II diabetic humans)

L64 ANSWER 56 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1996:234410 HCAPLUS

DN 124:278164

TI Therapeutic effect of glibenclamide in a fixed **combination** with metformin or phenformin in NIDDM patients

AU Raptis, A. E.; Tountas, N. B.; Yalouris, A. G.; Halvatsiotis, P. G.; Raptis, S. A.

CS 2nd Dept. Int. Med.-Propaedeutic, Athens Univ. Med. Sch., Athens, Greece

SO Horm. Metab. Res. (1996), 28(2), 89-94
CODEN: HMMRA2; ISSN: 0018-5043

DT Journal

LA English

CC 1-5 (Pharmacology)

AB The **combination** of a sulfonylurea with a biguanide improves the pancreatic .beta.-cell insulin secretion and the insulin utilization in peripheral tissues in NIDDM. This open, crossover, randomized and prospective study was designed to compare the effects of the fixed **combination** glibenclamide-phenformin (GL-PHEN) - 2.5 and 25 mg resp., on NIDDM **diabetes** control. Thirty NIDDM patients, in ideal metabolic control, who were being treated with GL-PHEN were divided in two groups. One group received GL-PHEN for 12 wk followed by 12 wk treatment with GL-METF and the reverse treatment was given to the second group. A statistically significant decrease of post-prandial blood glucose ($p = 0.034$) and glycosylated hemo-globin ($p<0.02$) values was obsd. under GL-METF treatment compared to those with GL-PHEN. The values of lactic acid were within normal limits during both treatments. The insulin secretion after breakfast was similar with both drug compds. The BMI of the patients remained the same during a follow-up steady of 24 wk. Lipid metab. did not change significantly during the trial and the safety parameters (renal and liver function, full blood count) remained unchanged. In conclusion, the administration of GL-METF leads to better **diabetes** control in NIDDM patients compared to that of GL-PHEN.

ST glibenclamide metformin phenformin antibiotic **diabetes** mellitus

IT Antibiotics
(therapeutic effect of glibenclamide in a fixed **combination** with metformin or phenformin in NIDDM human patients)

IT **Diabetes** mellitus
(maturity-onset, therapeutic effect of glibenclamide in a fixed **combination** with metformin or phenformin in NIDDM human

patients)
IT 114-86-3, Phenformin **657-24-9**, Metformin **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(therapeutic effect of glibenclamide in a fixed **combination** with metformin or phenformin in NIDDM human patients)

L64 ANSWER 57 OF 92 MEDLINE
AN 97122686 MEDLINE
DN 97122686
TI [Comparative study of the efficiency of ultralente insulin and NPH insulin combined with sulfonylurea in type 2 diabetes patients with secondary tolerance to sulfonylurea. Possible selection criteria].
Studio comparato tra l'efficacia dell'insulina ultralenta e dell'insulina NPH in associazione alle sulfoniluree in pazienti diabetici di tipo 2 con fallimento secondario alle sulfoniluree. Possibili criteri di scelta.
AU Sangiorgio L; Rabuazzo M A; Cordaro G; Grasso G; Condorelli L; Lunetta M
CS Istituto di Medicina Interna Endocrinologia e Metabolismo, Universit`a degli Studi, Catania.
SO MINERVA ENDOCRINOLOGICA, (1996 Jun) 21 (2) 47-52.
Journal code: NAN. ISSN: 0391-1977.
CY Italy
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA Italian
EM 199704
EW 19970404
AB The treatment of NIDDM patients with secondary failure to sulfonylureas is still a debated problem. In this study we compared in NIDDM patients with secondary failure to glyburide, the effect of adding a single, **low -dose** bed time either NPH or ultralent insulin injection (0.15-0.2 U/kg) to the previously ineffective sulfonylurea treatment. Both NPH and ultralent insulin therapy have been demonstrated to be effective in ameliorating metabolic control in NIDDM patients with secondary failure to sulfonylureas. However, the addition of bed-time ultralent insulin caused a greater and significant decrease in post prandial plasma glucose. In contrast, the average fasting plasma glucose decrease was significantly greater after NPH insulin administration. These results indicate that in NIDDM patients with secondary failure to glyburide bed-time ultralent insulin administration is a better tool to improve the post prandial plasma glucose.
CT Check Tags: Comparative Study; Female; Human; Male
Blood Glucose: AN, analysis
C-Peptide: AN, analysis
Cross-Over Studies
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Drug Administration Schedule
Drug Therapy, Combination
Drug Tolerance
Eating
English Abstract
Fasting: BL, blood
*Glyburide: AD, administration & dosage
Glyburide: PD, pharmacology
Hemoglobin A, Glycosylated: AN, analysis
*Hypoglycemic Agents: AD, administration & dosage
Hypoglycemic Agents: PD, pharmacology
*Insulin, Isophane: AD, administration & dosage
Insulin, Isophane: PD, pharmacology
*Insulin, Lente: AD, administration & dosage
Insulin, Lente: PD, pharmacology
Middle Age

Treatment Outcome
RN **10238-21-8 (Glyburide)**; 53027-39-7 (Insulin, Isophane); 8049-62-5 (Insulin, Lente)
CN 0 (Blood Glucose); 0 (C-Peptide); 0 (Hemoglobin A, Glycosylated); 0 (Hypoglycemic Agents)

L64 ANSWER 58 OF 92 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 7
AN 1996:236235 HCAPLUS
DN 124:307161
TI Is metformin safe enough for ageing type 2 diabetic patients?
AU Gregorio, F.; Ambrosi, F.; Filipponi, P.; Manfrini, S.; Testa, I.
CS Dept. Internal Medicine, Pathology and Pharmacology, University Perugia, Fabriano, Italy
SO Diabetes Metab. (1996), 22(1), 43-50
CODEN: DIMEFW
DT Journal
LA English
CC 1-10 (Pharmacology)
AB We assessed the effect of adding **low doses** of metformin to sulfonylurea **therapy** in 76 elderly Type 2 diabetic patients by monitoring glycemic control and blood lactate for one year. Metformin markedly improved glycemic control. Fasting lactate concns. were not affected and post-meal lactate peaks were minimally increased. Addnl. benefits included an improvement in some lipid parameters, a redn. in serum uric acid and a significant wt. loss in overweight patients. Metformin was clin. well-tolerated. Instead of advanced age alone, renal function and/or any other age-related factor likely to contribute to lactate overprodn. should be the basis for deciding on metformin **therapy**. No evidence indicated that metformin should be denied a priori aging Type 2 diabetic patients.
ST **diabetes** hypoglycemic metformin
IT Antidiabetics and Hypoglycemics
(metformin safety for aging humans who are type 2 diabetic patients)
IT **Diabetes** mellitus
(maturity-onset, metformin safety for aging humans who are type 2 diabetic patients)
IT **657-24-9**, Metformin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metformin safety for aging humans who are type 2 diabetic patients)

L64 ANSWER 59 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:72594 HCAPLUS
DN 126:195077
TI Pharmacological blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivatives and biguanides
AU Lebedeva, E. A.
CS Dep. Endocrinol., Saratov State Medi. Univ., Saratov, 443099, Russia
SO Eksp. Klin. Farmakol. (1996), 59(5), 40-42
CODEN: EKFAE9; ISSN: 0869-2092
PB Izdatel'stvo Folium
DT Journal
LA Russian
CC 1-10 (Pharmacology)
AB A hypothesis is advanced, according to which substances contg. an amino group can compete with glucose in binding with protein groups and inhibiting in this way glycosylation. Screening in vitro expts. with nicotinic acid, nicotinamide, piracetam, panangin, ascorbic acid, bucarban, betanase, and adebit in a concn. of 10-3 M were performed. Bucarban, betanase, and adebit were found to be capable of inhibiting glycosylation. Daily oral administration of bucarban and adebit in **therapeutic doses** for one month **reduced** the blood fructosamine level in rats with alloxan **diabetes** without

changing the level of glycemia.
ST glycosylation **diabetes** sulfonylurea biguanide amino group; antidiabetic amino group contg drug glycosylation
IT Structure-activity relationship
(glycosylation-inhibiting; pharmacol. blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivs. and biguanides)
IT Amino group
Antidiabetic agents
Diabetes mellitus
Glycosylation
(pharmacol. blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivs. and biguanides)
IT Proteins (general), biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacol. blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivs. and biguanides)
IT 50-81-7, Ascorbic acid, biological studies 59-67-6, Nicotinic acid, biological studies 98-92-0, Nicotinamide 7491-74-9, Piracetam 8076-65-1, Panangin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(pharmacol. blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivs. and biguanides)
IT 339-43-5, Bucarban **10238-21-8**, Betanase 15537-73-2, Adebit
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pharmacol. blockade of protein glycosylation in **diabetes** mellitus with sulfonyl urea derivs. and biguanides)

L64 ANSWER 60 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 96290488 EMBASE
DN 1996290488
TI Oral antidiabetic drugs: An overview.
AU Melander A.
CS Medical Research Centre, Malmo General Hospital,S-214 01 Malmo, Sweden
SO Diabetic Medicine, (1996) 13/SUPPL. 6 (S143-S147).
ISSN: 0742-3071 CODEN: DIMEEV
CY United Kingdom
DT Journal; Conference Article
FS 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Chronic hyperglycaemia, i.e. impaired glucose tolerance (IGT) and NIDDM, conveys a great risk of macrovascular disease. Both insulin resistance and impaired insulin secretion seem necessary to establish chronic hyperglycaemia, and untreated it appears to promote and worsen both insulin resistance and impaired insulin secretion. The prevention and treatment of chronic hyperglycaemia should include measures directed at both derangements, and the therapeutic goal should be normoglycaemia. As this is rarely achieved by non-pharmacologic treatment alone, addition of oral antidiabetic drugs are often indicated. Their ability to attain euglycaemia is greater the earlier they are employed, but they should never be introduced until after optimization of non-pharmacologic measures. Delayed early insulin response to glucose or a meal always accompanies chronic hyperglycaemia and is not normalized by non-pharmacologic treatment. This justifies the use of insulin-releasing drugs with a rapid onset of action, e.g. the sulphonylurea glipizide. The non-sulphonylureas, repaglinide and A-4166, are even more rapid- and also short-acting, representing a reduced risk of long-lasting, and hence

dangerous, hypoglycaemia. Continuous exposure to high concentrations of sulphonylureas may down-regulate beta-cell sensitivity. Maximum **doses** are much **lower** than previously assumed. The most effective improvers of insulin action seem to be the thiazolidinediones, but they are not yet marketed. Metformin is the only globally available drug for improving insulin action. It is as antihyperglycaemic as sulphonylureas but does not cause hyperinsulinaemia, weight increase or hypoglycaemia. The risk of lactic acidosis can be minimized by avoiding metformin in subjects with renal impairment. Combined treatment with sulphonylurea and metformin can be highly effective even in advanced NIDDM.

CT Medical Descriptors:
*diet therapy
***impaired glucose tolerance**
***non insulin dependent diabetes mellitus: TH, therapy**
***non insulin dependent diabetes mellitus: DT, drug therapy**
conference paper
diarrhea
human
hyperglycemia: SI, side effect
Drug Descriptors:
*2,4 thiazolidinedione derivative: CM, drug comparison
*2,4 thiazolidinedione derivative: DT, drug therapy
*2,4 thiazolidinedione derivative: PD, pharmacology
*acarbose: PD, pharmacology
*acarbose: DT, drug therapy
*acarbose: CM, drug comparison
*biguanide derivative: DT, drug therapy
*biguanide derivative: PD, pharmacology
*biguanide derivative: AE, adverse drug reaction
*biguanide derivative: CM, drug comparison
*chlorpropamide: PD, pharmacology
*chlorpropamide: DT, drug therapy
*chlorpropamide: CM, drug comparison
*glibenclamide: DT, drug therapy
*glibenclamide: CM, drug comparison
*glibenclamide: PD, pharmacology
***glibenclamide: CB, drug combination**
*metformin: DT, drug therapy
*metformin: PD, pharmacology
*metformin: CM, drug comparison
***metformin: CB, drug combination**
*n (4 isopropylcyclohexylcarbonyl) dextro phenylalanine: CM, drug comparison
*n (4 isopropylcyclohexylcarbonyl) dextro phenylalanine: DT, drug therapy
*n (4 isopropylcyclohexylcarbonyl) dextro phenylalanine: PD, pharmacology
*oral antidiabetic agent: DT, drug therapy
*oral antidiabetic agent: PD, pharmacology
*oral antidiabetic agent: CM, drug comparison
*repaglinide: PD, pharmacology
*repaglinide: DT, drug therapy
*repaglinide: CM, drug comparison
*sulfonylurea derivative: DT, drug therapy
*sulfonylurea derivative: AE, adverse drug reaction
*sulfonylurea derivative: CM, drug comparison
*sulfonylurea derivative: DO, drug dose
*sulfonylurea derivative: PD, pharmacology

RN (acarbose) 56180-94-0; (chlorpropamide) 94-20-2; (glibenclamide) **10238-21-8**; (metformin) **1115-70-4, 657-24-9**; (n (4 isopropylcyclohexylcarbonyl) dextro phenylalanine) 105746-37-0, 105816-04-4, 105816-06-6; (repaglinide) 135062-02-1

CN A 4166

L64 ANSWER 61 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1995:876418 HCAPLUS
DN 123:329743
TI Clinical profile of glimepiride
AU Draeger, Eberhard
CS Clinical Research, Hoechst AG, Frankfurt/Main, 65926, Germany
SO Diabetes Res. Clin. Pract. (1995), 28(Suppl.), S139-S146
CODEN: DRCPE9; ISSN: 0168-8227
DT Journal
LA English
CC 1-10 (Pharmacology)
AB In order to achieve appropriate blood glucose control, the treatment of non-insulin dependent (NIDDM) Type II **diabetes** usually starts with diet and exercise. If this still results in insufficient metabolic control, oral hypoglycemic drugs or insulin are added to the non-pharmacol. measures. Sulfonylureas have been used successfully as oral hypoglycemic agents since the 1950s but there are aspects where medication could be better adjusted to the patient's needs. Preclin. investigations on animals and in vitro studies with glimepiride (HOE490), a new sulfonylurea, suggested some benefit over sulfonylureas currently available, including **lower dosage**, rapid onset and long duration of action, lower insulin and C-peptide levels, possibly due to less stimulation of insulin secretion and more pronounced extrapancreatic effects. The clin. relevance of these findings were studied in clin. trials. 19 Phase II and 4 phase III clin. studies, in a total of about 3750 Type II diabetic patients, established efficacy and safety of glimepiride in comparison to placebo and glibenclamide and showed its **therapeutic** value. 1 Mg per day induced a marked blood glucose redn. (FPG 2.4 mmol/l; HbA1c 1.2%) which could be enhanced by increasing the **dose** to the max. effective 4 and 8 mg daily. In patients, glimepiride had a more rapid onset of action than glibenclamide, with a long duration of action. Glimepiride achieved metabolic control with the **lowest dose** (1-8 mg daily) of all the sulfonylureas. In addn., it maintained a more physiol. regulation of insulin secretion than glibenclamide during phys. exercise, suggesting that there may be less risk of hypoglycemia with glimepiride. Large phase III studies were designed to characterize the product under conditions which were to be as close as possible to every-day life oral **therapy** of Type II **diabetes**. These long-term, glibenclamide-controlled studies showed that equiv. metabolic control was achieved with a **dose range** of 1-8 mg glimepiride given once daily and 2.5-20 mg glibenclamide daily (given as divided **dose** at the higher **dose** levels). This equiv. metabolic control was achieved with lower insulin concns. (median difference: -0.92 .mu.U/mL; P = 0.04) and C-peptide (median difference: -0.14 ng/mL; P = 0.03) with glimepiride. Glimepiride was well tolerated and fewer episodes of hypoglycemia were obsd. in the glimepiride group than in the glibenclamide group. In conclusion, glimepiride showed a no. of improvements over currently available sulfonylureas that may provide clin. benefit to patients with NIDDM.
ST glimepiride glibenclamide antidiabetic
IT Antidiabetics and Hypoglycemics
(clin. profile of glimepiride in humans)
IT **10238-21-8**, Glibenclamide 93479-97-1, Glimepiride
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(clin. profile of glimepiride in humans)

L64 ANSWER 62 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 95138012 EMBASE
DN 1995138012
TI Metformin: A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus.
AU Dunn C.J.; Peters D.H.
CS Adis International Limited, 41 Centorian Drive,Mairangi Bay, Auckland 10,

New Zealand
SO Drugs, (1995) 49/5 (721-749).
ISSN: 0012-6667 CODEN: DRUGAY
CY New Zealand
DT Journal; General Review
FS 003 Endocrinology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The biguanide metformin (dimethylbiguanide) is an oral antihyperglycaemic agent used in the management of non-insulin-dependant diabetes mellitus (NIDDM). It reduces blood glucose levels, predominantly by improving hepatic and peripheral tissue sensitivity to insulin without affecting the secretion of this hormone. Metformin also appears to have potentially beneficial effects on serum lipid levels and fibrinolytic activity although the long term clinical implications of these effects are unclear. Metformin possesses similar antihyperglycaemic efficacy to sulphonylureas in obese and nonobese patients with NIDDM. Additionally, interim data from the large multicentre United Kingdom Prospective Diabetes Study (UKPDS) indicated similar antihyperglycaemic efficacy for metformin and insulin in newly diagnosed patients with NIDDM. Unlike the sulphonylureas and insulin, however, metformin treatment is not associated with increased bodyweight. Addition of metformin to existing antidiabetic therapy confers enhanced antihyperglycaemic efficacy. This may be of particular use in improving glycaemic control in patients with NIDDM not adequately controlled with sulphonylurea monotherapy, and may serve to reduce or eliminate the need for daily insulin injections in patients with NIDDM who require this therapy. The acute, reversible gastrointestinal adverse effects seen with metformin may be minimised by administration with or after food, and by using **lower dosages**, increased
slowly where necessary. Lactic acidosis due to metformin is rare, and the risk of this complication may be minimised by observance of prescribing precautions and contraindications intended to avoid accumulation of the drug or lactate in the body. Unlike the sulphonylureas, metformin does not cause hypoglycaemia. Thus, metformin is an effective antihyperglycaemic agent which appears to improve aberrant plasma lipid and fibrinolytic profiles associated with NIDDM. Possible long term clinical benefits of this drug with regard to cardiovascular mortality and morbidity are not yet established but are being assessed in a major ongoing study. Since metformin does not promote weight gain or hypoglycaemia it should be considered first-line pharmacotherapy in obese patients with NIDDM inadequately controlled by nonpharmacological measures. Metformin appears similarly effective for the pharmacological management of NIDDM in nonobese patients.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
abdominal discomfort: SI, side effect
anorexia: SI, side effect
cardiovascular system
cholesterol blood level
clinical trial
crossover procedure
diarrhea: SI, side effect
double blind procedure
drug absorption
drug contraindication
drug distribution
drug efficacy
drug excretion
drug metabolism
drug safety
gastrointestinal symptom: SI, side effect
gluconeogenesis

glucose metabolism
glucose utilization
human
insulin blood level
lactic acidosis: SI, side effect
lipid metabolism
megaloblastic anemia: SI, side effect
multicenter study
nausea: SI, side effect
normal human
oral drug administration
pneumonia: SI, side effect
pregnancy
randomized controlled trial
review
taste disorder: SI, side effect
triacylglycerol blood level
vasculitis: SI, side effect
Drug Descriptors:
insulin receptor
acarbose: IT, drug interaction
chlorpropamide: CM, drug comparison
chlorpropamide: DT, drug therapy
cholesterol: EC, endogenous compound
cimetidine: IT, drug interaction
glibenclamide: DT, drug therapy
glibenclamide: CM, drug comparison
glibenclamide: CB, drug combination
gliclazide: DT, drug therapy
gliclazide: CM, drug comparison
gliclazide: CB, drug combination
glipizide: CM, drug comparison
glipizide: CB, drug combination
glipizide: DT, drug therapy
gliquidone: DT, drug therapy
gliquidone: CB, drug combination
gliquidone: CM, drug comparison
glucose: EC, endogenous compound
glucose transporter: EC, endogenous compound
guar gum: CM, drug comparison
guar gum: DT, drug therapy
insulin: DT, drug therapy
insulin: CM, drug comparison
insulin: CB, drug combination
insulin: EC, endogenous compound
metformin: CB, drug combination
metformin: AE, adverse drug reaction
metformin: PD, pharmacology
metformin: PK, pharmacokinetics
metformin: DT, drug therapy
metformin: IT, drug interaction
metformin: DO, drug dose
metformin: CM, drug comparison
phenprocoumon: PK, pharmacokinetics
phenprocoumon: IT, drug interaction
phenprocoumon: DO, drug dose
sulfonylurea: CB, drug combination
sulfonylurea: DT, drug therapy
triacylglycerol: EC, endogenous compound
RN (acarbose) 56180-94-0; (chlorpropamide) 94-20-2; (cholesterol) 57-88-5; (cimetidine) 51481-61-9, 70059-30-2; (glibenclamide) **10238-21-8**; (gliclazide) 21187-98-4; (glipizide) 29094-61-9; (gliquidone) 33342-05-1; (glucose) 50-99-7, 84778-64-3; (guar gum) 9000-30-0; (insulin) 9004-10-8; (metformin) **1115-70-4, 657-24-9**; (phenprocoumon)

435-97-2

L64 ANSWER 63 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:942488 HCAPLUS
DN 124:45372
TI Efficacy of metformin in patients with non-insulin-dependent **diabetes** mellitus
AU DeFronzo, Ralph A.; Goodman, Anita M.; et al.
CS Health Science Center, University Texas, San Antonio, TX, 78284, USA
SO N. Engl. J. Med. (1995), 333(9), 541-9
CODEN: NEJMAG; ISSN: 0028-4793
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Sulfonylurea drugs have been the only oral therapy available for patients with non-insulin-dependent **diabetes** mellitus (NIDDM) in the United States. Recently, however, metformin has been approved for the treatment of NIDDM. We performed two large, randomized, parallel-group, double-blind, controlled studies in which metformin or another treatment was given for 29 wk to moderately obese patients with NIDDM whose **diabetes** was inadequately controlled by diet (protocol 1: metformin vs. placebo; 289 patients), or diet plus glyburide (protocol 2: metformin and glyburide vs. metformin vs. glyburide; 632 patients). To det. efficacy we measured plasma glucose (while the patients were fasting and after the oral administration of glucose), lactate, lipids, insulin, and glycosylated Hb before, during, and at the end of the study. In protocol 1, at the end of the study the 143 patients in the metformin group, as compared with the 146 patients in the placebo group, had lower mean (.+-.SE) fasting plasma glucose concns. (189.+-.5 vs. 244.+-.6 mg per dL [10.6.+-.0.3 vs. 13.7.+-.0.3 mmol per L], P<0.001) and glycosylated Hb values (7.1.+-.0.1 percent vs. 8.6.+-.0.2 percent, P<0.001). In protocol 2, the 213 patients given metformin and glyburide, as compared with the 209 patients treated with glyburide alone, had lower mean fasting plasma glucose concns. (187.+-.4 vs. 261.+-.4 mg per dL [10.5.+-.0.2 vs. 14.6.+-.0.2 mmol per L], P<0.001) and glycosylated Hb values (7.1.+-.0.1 percent vs. 8.7.+-.0.1 percent, P<0.001). The effect of metformin alone was similar to that of glyburide alone. Eighteen percent of the patients given metformin and glyburide had symptoms compatible with hypoglycemia, as compared with 3 percent in the glyburide group and 2 percent in the metformin group. In both protocols the patients given metformin had statistically significant decreases in plasma total and low-d. lipoprotein cholesterol and triglyceride concns., whereas the values in the resp. control groups did not change. There were no significant changes in fasting plasma lactate concns. in any of the groups. Metformin monotherapy and **combination** therapy with metformin and sulfonylurea are well tolerated and improve glycemic control and lipid concns. in patients with NIDDM whose **diabetes** is poorly controlled with diet or sulfonylurea therapy alone.
ST **diabetes** mellitus metformin sulfonylurea
IT Antidiabetics and Hypoglycemics
(efficacy of metformin in patients with non-insulin-dependent **diabetes** mellitus)
IT **657-24-9**, Metformin **10238-21-8**, Glyburide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of metformin in patients with non-insulin-dependent **diabetes** mellitus)

L64 ANSWER 64 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 95083958 EMBASE
DN 1995083958
TI Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients.
AU Chow C.-C.; Sorensen J.P.; Tsang L.W.W.; Cockram C.S.

CS Department of Medicine, Prince of Wales Hospital,Shatin, N.T., Hong Kong
SO Diabetes Care, (1995) 18/3 (307-314).
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Article
FS 006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB OBJECTIVES - Optimal insulin regimens for non-insulin dependent diabetes mellitus (NIDDM) patients with secondary failure are controversial. We evaluated the efficacy, side effects, and quality of life of patients receiving insulin either alone or in combination with their previous oral hypoglycemic agents (OHAs). RESEARCH DESIGN AND METHODS - Fifty-three Chinese patients with NIDDM (mean age 53.9 .+-. 12.6 years, duration of diabetes 9.0 .+-. 4.9 years, body wt 60. 4 .+-. 13.3 kg with corresponding body mass index 24.2 .+-. 43 kg/m2, receiving the maximum dose of sulfonylurea and/or metformin) were confirmed to have OHA failure. Twenty seven patients were randomized to continue OHAs and were given additional bedtime insulin (combination group); 26 patients were randomized to insulin therapy alone with twice-daily insulin (insulin group). Insulin doses were increased incrementally, aiming at fasting plasma glucose (FPG) <78 mmol/l during a stabilization period of up to 8 weeks. Insulin dosage, body weight, glycemic control, and quality of life were assessed before and at 3 and 6 months after stabilization. RESULTS - Both groups showed similar improvement of glycemic control. For the combination group, FPG decreased from 13.5 .+-. 2.7 to 8.9 .+-. 3.0 mmol/l at 3 months ($P < 0.0001$) and to 8.6 .+-. 2.5 mmol/l at 6 months ($P < 0.0001$). For the insulin group, FPG decreased from 13.5 .+-. 3.6 to 7.5 .+-. 3.0 mmol/l at 3 months ($P < 0.0001$) and to 9.8 .+-. 3.5 mmol/l at 6 months ($P < 0.0001$). No significant differences were observed between the groups. Similarly, both groups had significant improvement of fructosamine and glycosylated hemoglobin (HbA(1c)). Fructosamine fell from a mean of 458 to 365 .mu.mol/l at 3 months ($P < 0.0001$) and to 371 .mu.mol/l at 6 months ($P < 0.0001$) and from 484 to 325 .mu.mol/l at 3 months ($P < 0.0001$) and to 350 .mu.mol/l at 6 months ($P < 0.0001$) for the combination and insulin groups, respectively. HbA(1c) decreased from 10.2 to 8.4% at 3 months ($P < 0.0001$) and to 8.7% at 6 months ($P < 0.0001$) in the combination group and from 10.7 to 7.8% at 3 months ($P < 0.0001$) and to 8.4% at 6 months ($P < 0.0001$) in the insulin group. Despite similar improvement of glycemia, insulin requirements were very different. At 3 months, the combination group was receiving a mean of 14.4 U/day compared with 57.5 U/day in the insulin group ($P < 0.0001$). Similar findings were observed at 6 months (15.0 vs. 57.2 U/day, $P < 0.0001$). Both groups gained weight. However, for the combination group, weight gain was 1.6 .+-. 1.8 kg at 3 months and 2.1 .+-. 2.5 kg at 6 months (both $P < 0.0001$ vs. baseline), whereas for the insulin group, weight gain was 3.5 .+-. 4.3 and 5.2 .+-. 4.1 kg, respectively (both $P < 0.0001$ vs. baseline). Weight gain was significantly greater in the insulin group ($P < 0.05$ at 3 months, and $P < 0.005$ at 6 months). Fasting plasma triglyceride decreased in the insulin group (1.8 .+-. 1.0 to 1.4 .+-. 0.8 mmol/l at 3 months [$P < 0.005$] and to 1.4 .+-. 0.7 mmol/l at 6 months [$P < 0.02$]) but not in the combination group. No changes were observed in total and high-density lipoprotein cholesterol. No severe hypoglycemic reactions were recorded in either group. Mild reactions occurred with similar frequency in both groups. Well-being and quality of life improved significantly in both groups. The majority of patients (82.7%) wanted to continue insulin beyond 6 months, irrespective of the treatment group. CONCLUSIONS - in NIDDM patients with secondary OHA failure, therapy with a combination of OHAs and insulin and with insulin alone was equally effective and well tolerated. However, combination therapy was associated with a **lower** insulin **dose** and less weight gain. Combination treatment may be considered when OHA failure occurs as a potential intermediate stage before full insulin replacement.

CT Medical Descriptors:
*insulin treatment
***non insulin dependent diabetes mellitus: DT, drug therapy**
adult
aged
article
cholesterol blood level
clinical trial
controlled study
drug efficacy
female
glucose blood level
human
hypoglycemia: SI, side effect
injection pain: SI, side effect
major clinical study
male
oral drug administration
quality of life
randomized controlled trial
subcutaneous drug administration
treatment failure
treatment outcome
triacylglycerol blood level
wellbeing
Drug Descriptors:
*insulin: DT, drug therapy
***insulin: CB, drug combination**
*insulin: CM, drug comparison
*insulin: DO, drug dose
*insulin: CT, clinical trial
*insulin: AE, adverse drug reaction
*oral antidiabetic agent: CT, clinical trial
*oral antidiabetic agent: AE, adverse drug reaction
***oral antidiabetic agent: CB, drug combination**
*oral antidiabetic agent: CM, drug comparison
*oral antidiabetic agent: DO, drug dose
*oral antidiabetic agent: DT, drug therapy
c peptide: EC, endogenous compound
cholesterol: CR, drug concentration
cholesterol: EC, endogenous compound
fructosamine: EC, endogenous compound
glibenclamide: DT, drug therapy
glibenclamide: DO, drug dose
glibenclamide: CM, drug comparison
glibenclamide: AE, adverse drug reaction
glibenclamide: CT, clinical trial
glibenclamide: CB, drug combination
gliclazide: AE, adverse drug reaction
gliclazide: CM, drug comparison
gliclazide: CT, clinical trial
gliclazide: CB, drug combination
gliclazide: DO, drug dose
gliclazide: DT, drug therapy
glipizide: CB, drug combination
glipizide: CT, clinical trial
glipizide: DT, drug therapy
glipizide: DO, drug dose
glipizide: CM, drug comparison
glipizide: AE, adverse drug reaction
hemoglobin a1c: EC, endogenous compound
human insulin: CB, drug combination
human insulin: DO, drug dose
human insulin: CM, drug comparison

human insulin: CT, clinical trial
human insulin: AE, adverse drug reaction
human insulin: DT, drug therapy
isophane insulin: CT, clinical trial
isophane insulin: AE, adverse drug reaction
isophane insulin: CB, drug combination
isophane insulin: DO, drug dose
isophane insulin: DT, drug therapy
isophane insulin: CM, drug comparison
low density lipoprotein cholesterol: CR, drug concentration
low density lipoprotein cholesterol: EC, endogenous compound
metformin: AE, adverse drug reaction
metformin: DT, drug therapy
metformin: DO, drug dose
metformin: CM, drug comparison
metformin: CB, drug combination
metformin: CT, clinical trial
triacylglycerol: EC, endogenous compound
triacylglycerol: CR, drug concentration

RN (insulin) 9004-10-8; (c peptide) 59112-80-0; (cholesterol) 57-88-5; (fructosamine) 4429-04-3; (glibenclamide) **10238-21-8**; (gliclazide) 21187-98-4; (glipizide) 29094-61-9; (hemoglobin a1c) 62572-11-6; (human insulin) 11061-68-0; (isophane insulin) 9004-17-5; (metformin) **1115-70-4, 657-24-9**
CN (1) Protaphane; Actraphane
CO (1) Novo nordisk

L64 ANSWER 65 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:688040 HCAPLUS
DN 123:102495
TI Effects of the biguanide metformin on splanchnic blood flow in rats: preferential and dose-dependent increase in islet blood flow
AU Jansson, Leif
CS Department Medical Cell Biology, Uppsala University, Uppsala, Swed.
SO Pharmacology (1995), 51(1), 43-7
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The aim of the present study was to evaluate if metformin, a biguanide used in the treatment of noninsulin-dependent **diabetes**, induced any changes in splanchnic circulation. For this purpose, anesthetized rats were injected i.p. with saline alone (1 mL/kg BW) or metformin (15 or 30 mg/kg BW) 30 min before blood flow measurements. No effects on blood glucose or serum insulin concns. could be discerned after administration of metformin. Both duodenal, whole pancreatic and islet blood flow were approx. doubled by the **lowest dose** (15 mg/kg BW) metformin. However, the higher dose (30 mg/kg BW) did not affect duodenal or pancreatic blood flow, whereas islet blood flow was markedly increased also in this group of animals. It is concluded that the blood flow to the pancreatic islets can be specifically enhanced by metformin. To what extent this contributes to the antihyperglycemic action of the drug is presently unknown.
ST metformin splanchnic pancreas islet circulation antihyperglycemic
IT Antidiabetics and Hypoglycemics
Pancreatic islet of Langerhans
(biguanide metformin effect on splanchnic and pancreatic islets blood flow in relation to antihyperglycemic action mechanism)
IT Circulation
(splanchnic, biguanide metformin effect on splanchnic and pancreatic islets blood flow in relation to antihyperglycemic action mechanism)
IT **657-24-9**, Metformin
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(biguanide metformin effect on splanchnic and pancreatic islets blood flow in relation to antihyperglycemic action mechanism)
IT 50-99-7, Glucose, biological studies 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(biguanide metformin effect on splanchnic and pancreatic islets blood flow in relation to antihyperglycemic action mechanism)

L64 ANSWER 66 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 94307669 EMBASE
DN 1994307669
TI Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: A double-blind controlled study.
AU Hermann L.S.; Schersten B.; Bitzen P.-O.; Kjellstrom T.; Lindgarde F.; Melander A.
CS Kulperod 2958,442 95 Kungaly, Sweden
SO Diabetes Care, (1994) 17/10 (1100-1109).
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Article
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB OBJECTIVE - To assess and compare the therapeutic efficacy and safety of metformin (M) and sulfonylurea (glyburide, G), alone and in various combinations, in patients with noninsulin-dependent diabetes mellitus (NIDDM). RESEARCH DESIGN AND METHODS - Of 165 patients (fasting blood glucose [FBG] .gtoreq.6.7 mmol/l) initially treated with diet alone, 144 (FBG still .gtoreq.6.7 mmol/l) were randomized to double-blind, double-dummy controlled treatment with M, G, or primary combination therapy (MG). The dose was titrated, with FBG <6.7 mmol/l as target, using, at most, six dose levels. The first three dose levels comprised increasing single-drug therapy (M or G) or primary combination at increasing but **low dosage** (MGL), and the second three levels were composed of various high-dose combinations, i.e., add-on therapy (M/G or G/M) and primary combination escalated to high dosage (MGH). Medication was maintained for 6 months after completed dose titration. RESULTS - The FBG target was achieved in 9% of patients after diet alone. Single-drug therapy was insufficient in 36% and MGL in 25% (NS) of the randomized patients. There was further improvement in glucose control by the high-dose combinations. Mean FBG .+-. SE was reduced (P = 0.001) from 9.1 .+-. 0.4 to 7.0 .+-. 0.2 mmol/l in those maintained on single-drug treatment or **low-dose** primary combination. Those treated with different high-dose combinations had a large mean FBG reduction, from 13.3 .+-. 0.8 to 7.8 .+-. 0.6 mmol/l. HbA(1c) levels showed corresponding reductions, and glycemic levels rose after drug discontinuation. Fasting C-peptide rose during treatment with G and MGL but not with M, while fasting insulin was not significantly changed. Meal-stimulated C-peptide and insulin levels were unchanged by M but increased by G and, to a lesser extent, by MGL. There were no significant insulin or C- peptide differences between the different high-dose combinations (M/G, G/M, and MGH). Body weight did not change following treatment with M or combination but increased by 2.8 .+-. 0.7 kg following G alone. Blood pressure was unchanged. Overall effects on plasma lipids were small, with no significant differences between groups. Drug safety was satisfactory, even if the reporting of (usually modest) adverse events was high; the profile, but not the frequency, differed between groups. CONCLUSIONS - Dose-effect titrated treatment with either metformin or glyburide promotes equal degrees of glycemic control. The former, but not the latter, is able to achieve this control without increasing body weight or hyperinsulinemia. Near-normal glycemia can be obtained by a combination of

metformin and sulfonylurea, even in advanced NIDDM.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
adult
aged
article
clinical trial
controlled study
dose response
double blind procedure
drug efficacy
drug safety
female
gastrointestinal symptom: SI, side effect
glucose blood level
human
hyperlactatemia: SI, side effect
hypertension: DT, drug therapy
hypoglycemia: SI, side effect
insulin blood level
ischemic heart disease: DT, drug therapy
lactate blood level
lipid blood level
major clinical study
male
neurological complication: SI, side effect
oral drug administration
randomized controlled trial
Drug Descriptors:
*glibenclamide: AE, adverse drug reaction
*glibenclamide: CM, drug comparison
*glibenclamide: DO, drug dose
***glibenclamide: CB, drug combination**
*glibenclamide: CT, clinical trial
*glibenclamide: DT, drug therapy
*metformin: CT, clinical trial
*metformin: AE, adverse drug reaction
*metformin: DT, drug therapy
*metformin: DO, drug dose
*metformin: CM, drug comparison
***metformin: CB, drug combination**
*sulfonylurea: DT, drug therapy
*sulfonylurea: DO, drug dose
*sulfonylurea: CM, drug comparison
***sulfonylurea: CB, drug combination**
*sulfonylurea: CT, clinical trial
*sulfonylurea: AE, adverse drug reaction
apolipoprotein a1: EC, endogenous compound
apolipoprotein b: EC, endogenous compound
beta adrenergic receptor blocking agent: DT, drug therapy
c peptide: EC, endogenous compound
cholesterol: EC, endogenous compound
diuretic agent: DT, drug therapy
glucose: EC, endogenous compound
glycosylated hemoglobin: EC, endogenous compound
high density lipoprotein cholesterol: EC, endogenous compound
insulin: EC, endogenous compound
lactic acid: EC, endogenous compound
low density lipoprotein cholesterol: EC, endogenous compound
placebo: CM, drug comparison
triacylglycerol: EC, endogenous compound
RN (glibenclamide) **10238-21-8**; (metformin) **1115-70-4, 657-24-9**; (c peptide) 59112-80-0; (cholesterol) 57-88-5; (glucose) 50-99-7, 84778-64-3; (glycosylated hemoglobin) 9062-63-9; (insulin)

9004-10-8; (lactic acid) 113-21-3, 50-21-5
CO Lipha (United Kingdom); Boehringer mannheim (Sweden)

L64 ANSWER 67 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 94152786 EMBASE
DN 1994152786
TI [Treatment of diabetes in the doctor's office - Current requirements - Part 2: Oral antidiabetic agents and treatment with insulin]. DIABETESBEHANDLUNG IN DER PRAXIS - HEUTIGE ANFORDERUNGEN. TEIL 2: ORALE ANTIDIABETIKA UND INSULINTHERAPIE.
AU Mehnert H.
CS Institut fur Diabetesforschung, Krankenhaus Schwabing, Kolner Platz 1,D-80804 Munchen, Germany
SO Fortschritte der Medizin, (1994) 112/12 (33-34+37-38).
ISSN: 0015-8178 CODEN: FMDZAR
CY Germany
DT Journal; (Short Survey)
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LA German
SL English; German
AB Oral antidiabetic agents continue to play an important role in the treatment of type 2 diabetes. Of decisive importance is the timing of their use, together with a knowledge of their specific properties. Acarbose, which needs to be initiated at a **low**, slowly increasing **dose**, is noted for the fact that it has virtually no systemic side effects. Metformin reduces plasma glucose levels without inducing hyperinsulinemia, and carries virtually no risk of lactic acidosis. Glibenclamide can be used either alone to treat type 2 diabetes or in combination with other oral antidiabetics or insulin. Today, intensified insulin therapy represents the optimal standard of insulin replacement. It permits meal-oriented injection of normal insulin and the use of longer-acting insulin overnight. This form of treatment is now facilitated by the possibilities of plasma glucose selfmonitoring and the use of injection aids (pen). Intensified treatment should be initiated at the time type I diabetes is diagnosed. In the case of a particularly instable metabolic situation or neuropathy, it may become necessary to use insulin pumps.
CT Medical Descriptors:
***diabetes mellitus: DT, drug therapy**
gastrointestinal disease: SI, side effect
human
hyperinsulinemia: SI, side effect
hypoglycemia: SI, side effect
oral drug administration
short survey
Drug Descriptors:
*antidiabetic agent: AE, adverse drug reaction
*antidiabetic agent: PD, pharmacology
***antidiabetic agent: CB, drug combination**
*antidiabetic agent: CM, drug comparison
*antidiabetic agent: DT, drug therapy
***insulin: CB, drug combination**
*insulin: CM, drug comparison
*insulin: EC, endogenous compound
*insulin: DT, drug therapy
acarbose: AE, adverse drug reaction
acarbose: CB, drug combination
acarbose: CM, drug comparison
acarbose: DT, drug therapy
acarbose: PD, pharmacology
glibenclamide: CB, drug combination

glibenclamide: CM, drug comparison
glibenclamide: DT, drug therapy
glibenclamide: PD, pharmacology
glibenclamide: AE, adverse drug reaction
metformin: CB, drug combination
metformin: CM, drug comparison
metformin: DT, drug therapy
metformin: PD, pharmacology
metformin: AE, adverse drug reaction
sulfonylurea derivative: AE, adverse drug reaction
sulfonylurea derivative: PD, pharmacology
sulfonylurea derivative: DT, drug therapy
sulfonylurea derivative: CM, drug comparison
sulfonylurea derivative: CB, drug combination
RN (insulin) 9004-10-8; (acarbose) 56180-94-0; (glibenclamide) **10238-21-8**; (metformin) **1115-70-4, 657-24-9**

L64 ANSWER 68 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1993-320451 [40] WPIDS
DNC C1993-142585
TI Glucagon-like peptide-1-, amide, fragment, analogue or deriv. utilisation - by prepn. of medicament for treatment of diabetes in regimen contg. treatment with oral hypoglycaemic agent e.g. sulphonyl urea, for storing synergistic effect.
DC B04
IN EFENDIC, S; GUTNIAK, M; KIRK, O
PA (NOVO) NOVO-NORDISK AS; (EFEN-I) EFENDIC S; (GUTN-I) GUTNIAK M
CYC 45
PI WO 9318786 A1 19930930 (199340)* EN 21p A61K037-28
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AU BB BG BR CA CZ FI HU JP KP KR KZ LK MG MN MW NO NZ PL RO RU SD SK UA US VN
AU 9338888 A 19931021 (199407) A61K037-28
EP 631505 A1 19950104 (199506) EN A61K037-28
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
JP 07504670 W 19950525 (199529) A61K038-26
CN 1088835 A 19940706 (199532) A61K037-02
US 5631224 A 19970520 (199726) 6p A61K038-26
EP 631505 B1 19991215 (200003) EN A61K038-26
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
DE 69327309 E 20000120 (200011) A61K038-26
ADT WO 9318786 A1 WO 1993-DK99 19930318; AU 9338888 A AU 1993-38888 19930318; EP 631505 A1 EP 1993-907820 19930318, WO 1993-DK99 19930318; JP 07504670 W JP 1993-516182 19930318, WO 1993-DK99 19930318; CN 1088835 A CN 1993-104504 19930318; US 5631224 A WO 1993-DK99 19930318, US 1994-295913 19941013; EP 631505 B1 EP 1993-907820 19930318, WO 1993-DK99 19930318; DE 69327309 E DE 1993-627309 19930318, EP 1993-907820 19930318, WO 1993-DK99 19930318
FDT AU 9338888 A Based on WO 9318786; EP 631505 A1 Based on WO 9318786; JP 07504670 W Based on WO 9318786; US 5631224 A Based on WO 9318786; EP 631505 B1 Based on WO 9318786; DE 69327309 E Based on EP 631505, Based on WO 9318786
PRAI DK 1992-363 19920319
REP 1.Jnl.Ref; WO 8706941; WO 9011296; WO 9111457
IC ICM A61K037-02; A61K037-28; A61K038-26
ICS A61K031-155; A61K031-17; A61K031-445; C07K014-605
AB WO 9318786 A UPAB: 19931129
The glucagon-like peptide (GLP)-1(7-37), GLP-1(7-36) amide, or a peptide contg. a fragment of the GLP-1(7-37) sequence, or an analogue or functional deriv. of the peptide is used for the prepn. of a medicament for use in the treatment of diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent, e.g. **metformin** or (S)-(+)-2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl) phenyl) butyl)amino)-2-oxo ethyl) benzoic acid.

USE/ADVANTAGE - The combination treatment has a synergistic effect in the treatment of diabetes, esp. type 2 diabetes.

In an example, on 4 differing days the effect of either injecting **glibenclamide** (1mg i.v.) or infusing GLP-1(7-36)amide at 0.75 pmol/kg body wt. per min. or a combination of these was studied in the same gp. of 6 insulin treated obese NIDDM patients after eating a meal and compared to administration of saline as control.

Both GLP-1(7-36) amide and **glibenclamide** significantly increased meal-related C-peptide response and when administered in combination exerted a clear synergistic effect. The combination had no effect on glucagon response. Both **glibenclamide** and GLP-1(7-36)amide lowered the isoglycaemic meal-related insulin requirement (IMIR) and in combination, IMIR was as low as 2.7+/-0.7U.

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B04-C01G; B07-D05; B10-A08; B10-A13D; B10-A17; B12-C09; B12-H05

L64 ANSWER 69 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1993-196698 [24] WPIDS
CR 1993-189400 [24]; 1993-196699 [24]; 1993-197743 [25]
DNC C1993-087117
TI Oral administration forms for peptidic medicaments - contg. esp. insulin in matrix of gelatin, fractionated gelatin, collagen hydrolysate or gelatin deriv. which can dissolve in physiological condition.
DC B04
IN FREIDENREICH, J; SCHICK, U; WERRY, J; WUNDERLICH, J
PA (ALFA-N) ALFATEC-PHARMA GMBH
CYC 21
PI WO 9310767 A1 19930610 (199324)* DE 43p A61K009-51
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
DE 4140177 A1 19930609 (199324) 6p A61K031-18
DE 4140178 A1 19930609 (199324) 6p A61K031-405
AU 9230801 A 19930628 (199342) A61K009-51
EP 615444 A1 19940921 (199436) DE A61K009-51
R: AT BE CH DE DK ES FR GB GR IT LI NL PT SE
EP 615445 A1 19940921 (199436) DE A61K009-51
R: AT BE CH DE DK ES FR GB GR IT LI NL PT SE
DE 4140177 C2 19951221 (199604) 11p A61K031-18
EP 615444 B1 19960306 (199614) DE 18p A61K009-51
R: AT BE CH DE DK ES FR GB GR IT LI NL PT SE
DE 59205625 G 19960411 (199620) A61K009-51
ES 2085656 T3 19960601 (199629) A61K009-51
ES 2087565 T3 19960716 (199635) A61K009-51
AU 671964 B 19960919 (199645) A61K047-42
US 5614219 A 19970325 (199718) 11p A61K009-24
DE 4140178 C2 19980219 (199811) 7p A61K031-405
ADT WO 9310767 A1 WO 1992-DE1009 19921204; DE 4140177 A1 DE 1991-4140177 19911205; DE 4140178 A1 DE 1991-4140178 19911205; AU 9230801 A AU 1992-30801 19921204; EP 615444 A1 EP 1992-924546 19921204, WO 1992-DE1009 19921204; EP 615445 A1 EP 1992-924547 19921204, WO 1992-DE1010 19921204; DE 4140177 C2 DE 1991-4140177 19911205; EP 615444 B1 EP 1992-924546 19921204, WO 1992-DE1009 19921204; DE 59205625 G DE 1992-505625 19921204, EP 1992-924546 19921204, WO 1992-DE1009 19921204; ES 2085656 T3 EP 1992-924546 19921204; ES 2087565 T3 EP 1992-924547 19921204; AU 671964 B AU 1992-30801 19921204; US 5614219 A WO 1992-DE1009 19921204, US 1994-244691 19940913; DE 4140178 C2 DE 1991-4140178 19911205
FDT AU 9230801 A Based on WO 9310767; EP 615444 A1 Based on WO 9310767; EP 615445 A1 Based on WO 9310768; EP 615444 B1 Based on WO 9310767; DE 59205625 G Based on EP 615444, Based on WO 9310767; ES 2085656 T3 Based on EP 615444; ES 2087565 T3 Based on EP 615445; AU 671964 B Previous Publ. AU 9230801, Based on WO 9310767; US 5614219 A Based on WO 9310767
PRAI DE 1991-4140177 19911205; DE 1991-4140178 19911205; DE 1991-4140186

19911205; DE 1991-4140195 19911205; US 1992-876867 19920430
REP 2.Jnl.Ref; DE 3106984; EP 138216; EP 230654; JP 03086834; US 3312594; WO 8505029; WO 8903207; WO 8902307; AU 495261; EP 275796; EP 282020; EP 349428; FR 1259081; FR 2608427
IC ICM A61K009-24; A61K009-51; A61K031-18; A61K031-405; A61K047-42
ICS A61K009-08; A61K009-10; A61K009-16; A61K009-26; A61K009-28; A61K009-40; A61K037-26
AB WO 9310767 A UPAB: 19931116
An oral administration form for peptidic medicaments contains at least one peptidic medicament in a matrix capable of dissolving under physiological conditions and consisting of gelatin, fractionated gelatin, collagen hydrolysate or a gelatin deriv. and pharmaceutically conventional carriers and auxilliaries, so that the colloidal or dissolved peptidic medicament has a charge and the molecules of the matrix former have the opposite charge.

The medicament is insulin. The gelatine has m.wt. distribution max. at 104-107 D. The medicament is essentially microencapsulated in the gelatine. The application form is in layer form, with a synthetic or natural coating, esp. in the form of a coated tablet. A slow release form can be combined with a rapid release form, the outermost layer pref. contg. the slow-release form and the second layer or nucleus contg. the acute form.

USE/ADVANTAGE - The release system is suitable for rapid release and/or slow-release. The low resorption quotient of peptidic medicaments, esp. insulin in the gastrointestinal tract is significantly increased using these oral administration forms. The patient compliance is considerably greater than with injection forms. The choice of gelatin enables the medicament to be released in the small or large intestine, so that it is no longer decomposed by peptidases. Thus any peptidic medicament which would be enzymatically inactivated in the gastrointestinal tract can be used in this form.

Dwg.0/2
FS CPI
FA AB
MC CPI: B10-A10; B12-H05; B04-B04A6; B06-D01; B12-D07; B12-D09; B12-M10B; B04-B02D2; B04-C01; B12-M10

L64 ANSWER 70 OF 92 MEDLINE
AN 93356364 MEDLINE
DN 93356364
TI Metabolic effects of omega-3 fatty acids in type 2 (non-insulin-dependent) diabetic patients.
AU Pelikanova T; Kohout M; Valek J; Kazdova L; Base J
CS Postgraduate Medical and Pharmaceutical Institute, Prague, Czech Republic.
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1993 Jun 14) 683 272-8. Journal code: 5NM. ISSN: 0077-8923.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Cancer Journals; Priority Journals
EM 199311
AB The metabolic effects of a 3-week dietary supplement of a fish oil concentrate was examined in mildly obese, normotriglyceridemic men with non-insulin-dependent diabetes mellitus (NIDDM) treated with hypoglycemic agents (n = 20). Patients were randomized into two groups, receiving 15 ml per day of fish oil (Martens Oil, Norway) containing 3.1 g of omega-3 fatty acids (FA) (n = 10) or placebo (n = 10). Whereas fish oil led to the expected increase in the **ratio** of omega-3 to omega-6 FA in serum phospholipids, reflecting the increase in omega-3 FA intake, it did not alter fasting or mixed meal stimulated blood glucose, plasma insulin, and C-peptide concentrations. No changes in insulin action were noted, estimated by the metabolic clearance rates of glucose at plasma insulin

levels of approximately 100 microU/ml and 1,400 microU/ml during a hyperinsulinemic, isoglycemic clamp; no changes were seen in insulin binding to erythrocytes. We conclude that during short-term administration, no adverse effects of **low dose** fish oil on glucose homeostasis were found in mildly obese NIDDM patients treated with oral hypoglycemic agents.

CT Check Tags: Human; Male
Adult
Blood Glucose: ME, metabolism
C-Peptide: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: BL, blood**
Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy
Dietary Fats, Unsaturated: AD, administration & dosage
*Dietary Fats, Unsaturated: PD, pharmacology
Fatty Acids, Omega-3: AD, administration & dosage
*Fatty Acids, Omega-3: PD, pharmacology
Fish Oils: AD, administration & dosage
*Fish Oils: PD, pharmacology
Glyburide: TU, therapeutic use
Insulin: BL, blood
Kinetics
Middle Age
Obesity in Diabetes: BL, blood
Obesity in Diabetes: DT, drug therapy
Triglycerides: BL, blood

RN **10238-21-8 (Glyburide)**; 11061-68-0 (Insulin)

CN 0 (Blood Glucose); 0 (C-Peptide); 0 (Dietary Fats, Unsaturated); 0 (Fatty Acids, Omega-3); 0 (Fish Oils); 0 (Triglycerides)

L64 ANSWER 71 OF 92 HCAPLUS COPYRIGHT 2000 ACS

AN 1993:225361 HCAPLUS

DN 118:225361

TI Metformin for obese, insulin-treated diabetic patients: improvement in glycemic control and reduction of metabolic risk factors

AU Giugliano, D.; Quatraro, A.; Consoli, G.; Minei, A.; Ceriello, A.; De Rosa, N.; D'Onofrio, F.

CS 1st Fac. Med., Univ. Naples, Italy

SO Eur. J. Clin. Pharmacol. (1993), 44(2), 107-12
CODEN: EJCPAS; ISSN: 0031-6970

DT Journal

LA English

CC 1-10 (Pharmacology)

AB The efficacy and safety to metformin in the treatment of obese, non-insulin-dependent, diabetic subjects poorly controlled by insulin after secondary failure to respond to sulfonylureas has been investigated. Fifty insulin-treated, obese diabetics participated in this prospective, randomized double-blind six-month trial. After a four-week run-in period, during which all patients were given placebo single-blind, patients were randomly assigned to continue to receive placebo or to active treatment with metformin. At six months, there was a relevant and significant improvement in glycemic control in **diabetes** receiving the combined insulin-metformin treatment (decrease in glucose -4.1 mmol.cntdot.L-1; glycosylated Hb A1 decrease -1.84%). No significant changes were seen in diabetics receiving insulin and placebo. There was a significant decrease in blood lipids (triglyceride and cholesterol), an increase in HDL-cholesterol and a redn. in blood pressure in diabetics taking metformin. These pos. findings were most marked in the 14 diabetics who experienced a good response to metformin (glucose profile <10 mmol.cntdot.L-1), and were less marked but still significant in the remaining 13 diabetics, whose response to **therapy** was not so good (glucose profile > 10 mmol.cntdot.L-1). The fasting insulin level was significantly lower after six months of combined insulin-metformin treatment as shown by a 25% **redn.** in the daily **dose** of insulin (-21.6 U/day). Metformin was well tolerated by all diabetics.

Combining metformin with insulin in obese, insulin-treated and poorly controlled diabetics may represent a safe strategy to achieve better glycemic control with a redn. in certain metabolic risk factors assocd. with the increased incidence of cardiovascular disease in **diabetes** mellitus.

ST metformin insulin dependent **diabetes** obesity

IT Glycerides, biological studies
RL: BIOL (Biological study)
(blood, metformin effect on, in obese insulin-treated diabetics)

IT Blood sugar
(metformin effect on, in obese insulin-treated diabetics)

IT Hyperglycemia
(metformin **therapy** for, in obese insulin-treated diabetics)

IT Antidiabetics and Hypoglycemics
(metformin, in obese insulin-treated diabetics)

IT Obesity
(non-insulin-dependent diabetics with, metformin effect on glycemia and metabolic risk factors in)

IT **Diabetes** mellitus
(maturity-onset, metformin **therapy** for, in obese humans)

IT 57-88-5, Cholesterol, biological studies
RL: BIOL (Biological study)
(blood, metformin effect on, in obese insulin-treated diabetics)

IT 9004-10-8, Insulin, biological studies
RL: BIOL (Biological study)
(glycemia and metabolic risk factors response to metformin and, in obese insulin-treated diabetics)

IT **657-24-9**, Metformin
RL: BIOL (Biological study)
(glycemia and metabolic risk factors response to, in obese insulin-treated diabetics)

IT 9062-63-9D, Hb A1, glycosylated
RL: BIOL (Biological study)
(metformin effect on, in obese insulin-treated diabetics)

L64 ANSWER 72 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-096588 [52] WPIDS
DNC C1992-044806
TI Treatment of non-insulin dependent diabetes mellitus - using hypoglycaemic agent e.g. sulphonurea or biguanide and an amylin antagonist.
DC B05 C16 D16
IN COOPER, G J S; MOORE, C X
PA (AMYL-N) AMYLIN CORP; (AMYL-N) AMYLIN PHARM INC
CYC 20
PI WO 9203148 A 19920305 (199212)* 97p
RW: AT CH DE DK ES GB GR LU NL SE
W: CA DK FI JP NO SE
EP 495963 A1 19920729 (199231) EN 97p A61K037-02
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
ZA 9106422 A 19920729 (199235) 82p A61K000-00
US 5260275 A 19931109 (199346) 25p A61K037-02
JP 07502971 W 19950330 (199521) A61K038-00
EP 495963 A4 19930901 (199527)
ADT WO 9203148 A WO 1991-US5767 19910814; EP 495963 A1 EP 1991-914953 19910814, WO 1991-US5767 19910814; ZA 9106422 A ZA 1991-6422 19910814; US 5260275 A US 1990-567919 19900814; JP 07502971 W JP 1991-514528 19910814, WO 1991-US5767 19910814; EP 495963 A4 EP 1991-914953
FDT EP 495963 A1 Based on WO 9203148; JP 07502971 W Based on WO 9203148
PRAI US 1990-567919 19900814
REP 2.Jnl.Ref; EP 408294; WO 8906135; 1.Jnl.Ref; EP 289287; EP 309100; GB 8709871; GB 8720115
IC ICM A61K037-02; A61K038-00
ICS A61K031-155; A61K031-18; A61K037-43; A61K049-00

AB WO 9203148 A UPAB: 19951004
Treatment of non-insulin dependent (type 2) diabetes mellitus comprises admin. of (i) a hypoglycaemic agent (I) which increases plasma concn. of amylin (II; same as diabetes associated peptide described in UK Application 8709871) and (2) an amylin antagonist (III).
Pref. (I) is a sulphonylurea, esp. **glibenclamide** or tolbutamide. (I) and (III) are admin. together or separately.
Patients in whom (I) cause an increase in (II) levels are identified by (II) (II)-assay; particularly qualitative or (semi)quantitative immunoassay. The same procedure can be used to monitor/evaluate hypoglycaemic treatment (including use of biguanidine derivs., specifically **metformin**, which do not increase (II) levels). A method for evaluating and screening agents useful in treatment of hyperglycaemia or hyperamylinaemia comprises measuring their effect on (II) levels in an animal, cell culture (esp. MIT 5-15 beta islet cells) or a perfused pancreas. Opt. the effect of the agent on insulin secretion is also determined.
USE/ADVANTAGE - Addn. of (III) increases the hypoglycaemic effect of (I). (II), which causes abnormal insulin release and glycogen synthesis, is implicated in deposit of amyloid in the pancreas of diabetics and in loss of beta cell mass/A
0/10
Dwg.0/10
FS CPI
FA AB; DCN
MC CPI: B10-A10; C10-A10; B12-C09; C12-C09; B12-G01; C12-G01; B12-H05; C12-H05; D05-H09

L64 ANSWER 73 OF 92 MEDLINE DUPLICATE 8
AN 92362490 MEDLINE
DN 92362490
TI Comparison of combined therapies in treatment of secondary failure to glyburide.
AU Trischitta V; Italia S; Mazzarino S; Buscema M; Rabuazzo A M; Sangiorgio L; Squatrito S; Vigneri R
CS Cattedra di Endocrinologia, Universit`a di Catania, Ospedale Garibaldi, Italy..
SO DIABETES CARE, (1992 Apr) 15 (4) 539-42.
Journal code: EAG. ISSN: 0149-5992.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199211
AB OBJECTIVE--To compare the effectiveness of alternative combined treatments in patients with non-insulin-dependent diabetes mellitus (NIDDM) with secondary failure to sulfonylureas. RESEARCH DESIGN AND METHODS--A crossover study was carried out by randomly assigning 16 NIDDM patients to a combined treatment with the addition of either a single **low-dose** bedtime injection of 0.2 U/kg body wt NPH insulin or an oral three times a day administration of 1.5 g/day metformin to the previously ineffective glyburide treatment. RESULTS--Both combined therapies significantly (P less than 0.01) reduced fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and percentage of HbA1. The addition of metformin was more effective than the addition of insulin (P less than 0.01) in improving PPPG in the 8 patients with higher post-glucagon C-peptide levels. In contrast, the efficacy of neither combined therapy was related to patient age, age of diabetes onset, duration of the disease, percentage of ideal body weight, and FPG. The addition of insulin but not metformin caused a significant (P less than 0.01) increase of mean body weight. Neither combined treatment caused changes in serum cholesterol and triglyceride levels. No symptomatic hypoglycemic episode

was reported in any of the 16 patients. CONCLUSIONS--The addition of bedtime NPH insulin or metformin was effective in improving the glycemic control in most NIDDM patients with secondary failure to glyburide. The combination of metformin and sulfonylurea was more effective in reducing PPPG and did not induce any increase of body weight.

CT Check Tags: Comparative Study; Human
Blood Glucose: ME, metabolism
Body Weight
C-Peptide: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology
Drug Administration Schedule
Drug Therapy, Combination
Eating
Fasting
Glyburide: AD, administration & dosage
*Glyburide: TU, therapeutic use
Hemoglobin A, Glycosylated: AN, analysis
Insulin, Isophane: AD, administration & dosage
*Insulin, Isophane: TU, therapeutic use
Metformin: AD, administration & dosage
*Metformin: TU, therapeutic use
Middle Age
Obesity in Diabetes: DT, drug therapy
Obesity in Diabetes: PP, physiopathology

RN **10238-21-8 (Glyburide)**; 53027-39-7 (Insulin, Isophane); **657-24-9 (Metformin)**

CN 0 (Blood Glucose); 0 (C-Peptide); 0 (Hemoglobin A, Glycosylated)

L64 ANSWER 74 OF 92 MEDLINE DUPLICATE 9
AN 93170102 MEDLINE
DN 93170102
TI Morning or bed-time insulin with or without glibenclamide in elderly type 2 diabetic patients unresponsive to oral antidiabetic agents.
AU Niskanen L; Lahti J; Uusitupa M
CS Department of Clinical Nutrition, University of Kuopio, Finland..
SO DIABETES RESEARCH AND CLINICAL PRACTICE, (1992 Dec) 18 (3) 185-90.
Journal code: EBI. ISSN: 0168-8227.
CY Netherlands
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199305
AB We studied in a group of elderly (mean age 77 yr) non-obese Type 2 diabetic patients (n = 9) in a randomised, placebo-controlled prospective cross-over study of 8 months duration, the effects of substituting maximal sulfonylurea medication with a single injection of human zinc insulin taken either at bedtime (BTI) or morning (MI). All patients were poorly controlled with oral antidiabetic agents. After a 2-month regimen with either BTI or MI, a glibenclamide (GL, 3.5 mg/day) was given for an additional 2 months. Both insulin regimens decreased mean diurnal blood glucose and glycosylated HbA1c values to a similar extent (2.6-2.7%; p < 0.01-0.05), but with a **lower** daily insulin **dose** with BTI (0.30 +/- 0.03 IU/kg) as compared with MI (0.39 +/- 0.05 IU/kg; p < 0.01). A further improvement in metabolic control was observed in both groups after the introduction of GL; the mean reduction in glycosylated HbA1c was 1.4% for BTI and 0.7% for MI (p < 0.01 and 0.05, respectively), In conclusion, a subgroup of poorly controlled elderly Type 2 diabetic patients showed an improvement in metabolic control after a single injection of insulin despite discontinuation of maximal doses of oral antidiabetic agents. After 2 months of insulin treatment, a further improvement was achieved by a **low dose** of sulfonylurea

in these patients who were formerly considered unresponsive to oral antidiabetic agents.

CT Check Tags: Comparative Study; Human
Aged
Apolipoprotein A-I: AN, analysis
Apolipoproteins B: BL, blood
C-Peptide: BL, blood
Cholesterol: BL, blood
Diabetes Mellitus, Non-Insulin-Dependent: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Drug Administration Schedule
*Glyburide: TU, therapeutic use
Hypoglycemic Agents: TU, therapeutic use
Insulin: AD, administration & dosage
*Insulin: TU, therapeutic use
Lipoproteins, HDL Cholesterol: BL, blood
Middle Age
Prospective Studies
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: TU, therapeutic use
Treatment Failure
Triglycerides: BL, blood

RN **10238-21-8 (Glyburide)**; 11061-68-0 (Insulin); 57-88-5 (Cholesterol)

CN 0 (Apolipoprotein A-I); 0 (Apolipoproteins B); 0 (C-Peptide); 0 (Hypoglycemic Agents); 0 (Lipoproteins, HDL Cholesterol); 0 (Recombinant Proteins); 0 (Triglycerides)

L64 ANSWER 75 OF 92 MEDLINE
AN 92396894 MEDLINE
DN 92396894
TI Combination daytime chlorpropamide-metformin/bedtime insulin in the treatment of secondary failures in non insulin dependent diabetes.
AU Aguilar C A; Wong B; Gomez-Perez F J; Rull J A
CS Departamento de Diabetes y Metabolismo de Lipidos, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico, D.F..
SO REVISTA DE INVESTIGACION CLINICA, (1992 Jan-Mar) 44 (1) 71-6.
Journal code: SCH. ISSN: 0034-8376.
CY Mexico
DT Journal; Article; (JOURNAL ARTICLE)
LA English
EM 199212
AB OBJECTIVES. To determine the effectiveness of the combination therapy with daytime chlorpropamide-metformin and bedtime NPH insulin in the treatment of secondary failures in NIDDM and to study its effects on insulin secretion. DESIGN. Non randomized open study with a duration of two months. The patients were followed six months after ending the study. INSTITUTION. Department of Diabetes and Lipid Metabolism. Instituto Nacional de la Nutricion "Salvador Zubiran", Mexico City. CHARACTERISTICS OF THE PATIENTS. Nine patients (seven women and two men) were included. All had NIDDM and secondary failure to antidiabetic oral drugs. Their fasting plasma glucose was 14.5 +/- 2 mM/L and their HbA1c 13.37 +/- 2.9%. At the entry and at the end of the study a 5h-OGTT was done with assays of plasma glucose and C-peptide. TREATMENT. Chlorpropamide (375 mg/day) plus metformin (1200 mg/day) and bedtime insulin (0.1 U/kg/day). RESULTS. After two months on combination therapy, fasting plasma glucose and HbA1c levels were remarkably improved (decreases of 7.3 +/- 0.6 and 9.1 +/- 1.02 respectively, p less than 0.002). The insulin **dose** was small (6.77 +/- 2.09 U/day). Side effects were minimal and infrequent. During the 5h-OGTT, the mean glucose area under the curve also decreased. The insulin secretion did not change but the C-peptide/glucose **ratio** increased. At the end of the study, the insulin **dose** was tapered off and stopped when possible. The four patients with the best glycemic control during the study were able to suspend the bedtime insulin and

maintain a good control six months after the insulin suspension. CONCLUSIONS. The combination therapy is useful in the treatment of secondary failures in NIDDM. Its advantages are the very **low** mean daily insulin **dose** needed, the **low** incidence of side effects and, if a HbA1c less than 8.7% is achieved, the restoration of oral antidiabetic drugs efficacy. The very **low** insulin **dose** used in this study could be explained by complementary effects of metformin and bedtime insulin on hepatic glucose output and a putative decrease in peripheral resistance attributable both to sulfonylurea and metformin.

CT Check Tags: Female; Human; Male
Adult
Aged
***Chlorpropamide: AD, administration & dosage**
Chlorpropamide: TU, therapeutic use
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Drug Administration Schedule
Drug Therapy, Combination
***Insulin: AD, administration & dosage**
Insulin: TU, therapeutic use
***Metformin: AD, administration & dosage**
Metformin: TU, therapeutic use
Middle Age

RN 11061-68-0 (Insulin); **657-24-9 (Metformin)**; 94-20-2 (Chlorpropamide)

L64 ANSWER 76 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 91185572 EMBASE
DN 1991185572
TI Treatment of NIDDM patients with secondary failure to glyburide: comparison of the addition of either metformin or bed-time NPH insulin to glyburide.
AU Vigneri R.; Trischitta V.; Italia S.; Mazzarino S.; Rabuazzo M.A.; Squatrito S.
CS Cattedra di Endocrinologia dell' Universita di Catania, Ospedale Garibaldi, USL 34, Piazza S.M. di Gesu, 95123 Catania, Italy
SO Diabete et Metabolisme, (1991) 17/1 BIS (232-234). ISSN: 0338-1684 CODEN: DIMEDU
CY France
DT Journal; Conference Article
FS 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
LA English
SL French; English
AB In this study we compared, in 12 NIDDM patients with secondary failure to glyburide, the effect of adding either a single, **low-dose** bed time NPH insulin injection (0.2 U/Kg) or an oral metformin administration (500 mg x 3) to the previously ineffective sulfonylurea treatment. The addition of both insulin and metformin treatment significantly improved fasting plasma glucose, post-prandial plasma glucose and %HbA1. The effect of both combined therapies was already evident and maximal after 2 weeks of treatment. The addition of bed-time NPH insulin caused a greater decrease of fasting plasma glucose, although the difference with the addition of metformin was not significant. In contrast, the average post-prandial plasma glucose decrease was significantly greater after metformin addition. The addition of bed-time NPH insulin caused a significant increase in average body weight, while after metformin addition, average body weight was unchanged; no change in the average cholesterol and triglyceride level was observed after either combined therapies.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**

adult
body weight
clinical article
conference paper
controlled study
drug combination
drug effect
drug efficacy
glucose blood level
human
priority journal
Drug Descriptors:
*glibenclamide: PD, pharmacology
*glibenclamide: DT, drug therapy
***glibenclamide: CB, drug combination**
*isophane insulin: DT, drug therapy
***isophane insulin: CB, drug combination**
*isophane insulin: CM, drug comparison
*metformin: DT, drug therapy
***metformin: CB, drug combination**
*metformin: CM, drug comparison
RN (glibenclamide) **10238-21-8**; (isophane insulin) 9004-17-5; (metformin) **1115-70-4, 657-24-9**

L64 ANSWER 77 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-312219 [41] WPIDS
DNC C1990-135055
TI Oxidising-energising compsn. for use in treating **diabetes** - comprises flavine-adenine di nucleotide, enzyme or coenzyme, and opt. further carbohydrate metabolism enzyme.
DC B04 D16
IN DUMAS, T; SPILIADIS, A; STANCESCO, A
PA (STAN-I) STANCESCO A
CYC 2
PI US 4959212 A 19900925 (199041)*
CA 2025569 A 19920319 (199222)# A61K037-48
ADT US 4959212 A US 1988-209877 19880622
PRAI US 1988-209877 19880622
IC ICM A61K037-48
ICS A61K031-52; A61K037-62
AB US 4959212 A UPAB: 19930928
Non-toxic, oxidising energising compsn. suitable for use as an accelerator of the carbohydrate oxidative degradation metabolic process or of the direct oxidn. of glucose, and effective to reduce the blood glucose concn. in **diabetes**, comprises (by wt.): (A) 10-95% FAD; (B) 5-90% of a coenzyme or enzyme from flavine mononucleotide (FMN) abiquinone (UBQ) UTP, TPN, DPN, ATP, UDPG, GTP, glucose oxidase (GOD) or mixts.; and (C) 0% to less than 50% of an enzyme from fructose diphosphate aldolase, phosphofructokinase hexokinase, glucokinase, glucose 6-phosphate dehydrogenase, glucose phosphate isomerase, and/or D-glucose phosphotransferase.

Synergistic hypoglycaemic compsn. comprises (i) 1-100 mg. of the above compsn., and (ii) either insulin or a sulphonamidic **antidiabetic** drug (I) in hypoglycaemic . USE/ADVANTAGE - The oxidising compsn. can be used in cases of only mild insulin deficiency, permitting the postponement of the need to use **antidiabetic** drugs. When used together with **antidiabetic** drugs, the compsn. gives synergistic lowering of blood glucose levels, so that drug **doses** can be **reduced** or drugs avoided altogether, and/or carbohydrate intake can be increased. Dosage of compsn. is pref. 5-40, esp. 10-25 mg/day.
0/0
FS CPI
FA AB; DCN

MC CPI: B04-B02C; B04-B02D2; B04-B03B; B07-D06; B10-A08; B12-C09; B12-H05; D05-A02

L64 ANSWER 78 OF 92 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 91016796 EMBASE
DN 1991016796
TI Insulin use in NIDDM.
AU Genuth S.
CS 1 Mount Sinai Drive,Cleveland, OH 44106, United States
SO Diabetes Care, (1990) 13/12 (1240-1264).
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; General Review
FS 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The effects of insulin treatment on the pathophysiology of non-insulin-dependent diabetes mellitus (NIDDM) are reviewed herein. Short-term studies indicate variable and partial reduction in excessive hepatic glucose output, decrease in insulin resistance, and enhancement of .beta.-cell function. These beneficial actions may be due to a decrease in secondary glucose toxicity rather than a direct attack on the primary abnormality. Insulin should be used as initial treatment of new-onset NIDDM in the presence of ketosis, significant diabetes-induced weight loss (despite residual obesity), and severe hyperglycemic symptoms. In diet-failure patients, prospective randomized studies comparing insulin to sulfonylurea treatment show approximately equal glycemic outcomes or a slight advantage to insulin. A key goal of insulin therapy is to normalize the fasting plasma glucose level. In contrast to the conventional use of morning injections of intermediate- and long-acting insulin, preliminary studies suggest potential advantages of administering the same insulins only at bedtime. Obese patients may require several hundred units of insulin daily and still not achieve satisfactory control. In some, addition of a sulfonylurea to insulin may **reduce** hyperglycemia, the insulin **dose**, or both. However, long-term benefits from such combination therapy remain to be demonstrated conclusively. Established adverse effects of insulin treatment in NIDDM are hypoglycemia, particularly in the elderly, and weight gain. Self-monitoring of blood glucose can identify patients in whom excessive weight gain is caused by subtle hypoglycemia. Whether insulin causes weight gain by direct effects on appetite or energy utilization remains controversial. A potential adverse effect of insulin has been suggested by epidemiological studies showing associations between hyperinsulinemia or insulin resistance and increased risk for coronary artery disease, stroke, and hypertension. Although potential mechanisms for an atherogenic action of insulin exist, current evidence does not prove cause and effect and does not warrant withholding insulin therapy (or compromising on dosage) when it is needed.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: TH, therapy**
***non insulin dependent diabetes mellitus: DT, drug therapy**
atherosclerosis: SI, side effect
diet
drug effect
human
hypoglycemia: SI, side effect
priority journal
review
subcutaneous drug administration
weight gain
side effect

Drug Descriptors:
*insulin: PR, pharmaceutics
*insulin: DT, drug therapy
*insulin: CM, drug comparison
*insulin: DO, drug dose
***insulin: CB, drug combination**
*sulfonylurea derivative: CM, drug comparison
***sulfonylurea derivative: CB, drug combination**
*sulfonylurea derivative: DT, drug therapy
chlorpropamide: DT, drug therapy
chlorpropamide: CM, drug comparison
glibenclamide: CM, drug comparison
glibenclamide: CB, drug combination
glibenclamide: DT, drug therapy
metformin: DT, drug therapy
metformin: CB, drug combination
metformin: CM, drug comparison
tolazamide: DT, drug therapy
tolazamide: CM, drug comparison
tolbutamide: DT, drug therapy
tolbutamide: CM, drug comparison
RN (insulin) 9004-10-8; (chlorpropamide) 94-20-2; (glibenclamide) **10238-21-8**; (metformin) **1115-70-4, 657-24-9**; (tolazamide) 1156-19-0; (tolbutamide) 473-41-6, 64-77-7

L64 ANSWER 79 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:583364 HCAPLUS
DN 109:183364
TI Effect of chronic sulfonylurea treatment on the myocardium of insulin-dependent diabetic rats
AU Mozaffari, Mahmood S.; Wilson, Glenn L.; Schaffer, Stephen W.
CS Coll. Med., Univ. South Alabama, Mobile, AL, 36688, USA
SO Can. J. Physiol. Pharmacol. (1988), 66(12), 1481-6
CODEN: CJPPA3; ISSN: 0008-4212
DT Journal
LA English
CC 1-10 (Pharmacology)
AB Adult rats treated with high **doses** of streptozocin became progressively more hyperglycemic during the first month of the diabetic condition. Treatment of these rats with the sulfonylurea glyburide halted, and in some cases, reversed this process in a high percentage of the diabetics. Assocd. with the glyburide-mediated improvement in fasting blood glucose levels was an increase in myocardial glucose utilization and lactate prodn. The stimulation of myocardial glucose utilization by insulin was greater in glyburide-treated hearts, indicating that the hyperglycemic agent increased insulin responsiveness. The sulfonylurea also partially restored insulin sensitivity to the normal **range**. In agreement with previous studies, myocardial mech. function was significantly impaired in the diabetic heart. When treated with glyburide, the severity of the mech. defect was significantly less. The sulfonylurea also promoted an increase in myosin ATPase activity and a shift in the myosinisozyme pattern in favor of the most active V1 form. These results imply that glyburide **therapy** can provide benefit to the diabetic heart by improving energy metab. and promoting a shift in myosin towards the most active form.
ST sulfonylurea heart function insulin dependent **diabetes**
IT Myosins
RL: BIOL (Biological study)
(ATPase and isoenzymes of, of heart, in insulin-dependent **diabetes**, glyburide effect on)
IT Heart, metabolism
(metab. and function of, in insulin-dependent **diabetes**, glyburide improvement of)
IT **Diabetes** mellitus

(insulin-dependent, hyperglycemia and heart dysfunction in, glyburide treatment of)
IT Sulfonamides
RL: BIOL (Biological study)
(sulfonylureas, hyperglycemia and heart dysfunction in insulin-dependent **diabetes** improvement by)
IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(calcium-magnesium-dependent, of heart myosin, glyburide stimulation of, in insulin-dependent **diabetes**)
IT 50-21-5, biological studies
RL: FORM (Formation, nonpreparative)
(formation of, by heart in insulin-dependent **diabetes**, glyburide increase of)
IT 9004-10-8, Insulin, biological studies
RL: BIOL (Biological study)
(heart response to, glyburide enhancement of, in insulin-dependent **diabetes**)
IT **10238-21-8**, Glyburide
RL: BIOL (Biological study)
(hyperglycemia and heart dysfunction in insulin-dependent **diabetes** improvement by)
IT 50-99-7, Glucose, biological studies
RL: BIOL (Biological study)
(utilization of, by heart in insulin-dependent **diabetes**, glyburide increase of)

L64 ANSWER 80 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:113392 HCAPLUS
DN 106:113392
TI Smoothing effect of a new .alpha.-glucosidase inhibitor, BAY m 1099, on blood glucose profiles of sulfonylurea-treated type II diabetic patients
AU Arends, J.; Willms, B. H. L.
CS Fachklin. Diabetes Stoffwechselkrankh., Bad Lauterberg, D-3422, Fed. Rep. Ger.
SO Horm. Metab. Res. (1986), 18(11), 761-4
CODEN: HMMRA2; ISSN: 0018-5043
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The .alpha.-glucosidase [9001-42-7] inhibitor BAY m 1099 [72432-03-2], a deoxynojirimycin deriv., was studied in sulfonylurea-treated type-II diabetic patients by using a placebo-controlled double-blind cross-over design. Given in 2 daily doses the inhibitor smoothened the blood glucose profile by lowering postprandial blood glucose peaks. Fasting and daily mean blood glucose levels measured as the area under the blood glucose curves were however not influenced significantly. This might be due to the short duration of the treatment periods or the **low dosage** of the drug. Abdominal side effects were negligible. The potential use of BAY m 1099 in sulfonylurea treatment in type-II **diabetes** is discussed.
ST glucosidase inhibitor Bay m 1099 **diabetes**; sulfonylurea antidiabetes glucosidase inhibitor
IT Antidiabetics and Hypoglycemics
(sulfonylureas, blood sugar response to .alpha.-glucosidase inhibitor BAY m 1099 and, in humans)
IT Blood sugar
(.alpha.-glucosidase inhibitor BAY m 1099 and sulfonylureas effect on, in diabetic humans)
IT Sulfonamides
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(sulfonylureas, antidiabetic activity of, blood sugar response to .alpha.-glucosidase inhibitor BAY m 1099 and, in diabetic humans)

IT **10238-21-8**, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antidiabetic activity of, blood sugar response to .alpha.-glucosidase inhibitor BAY m 1099 and, in diabetic humans)
IT 72432-03-2, BAY m 1099
RL: BIOL (Biological study)
(blood sugar response to sulfonylureas and, in diabetic humans)
IT 9001-42-7, .alpha.-Glucosidase
RL: BIOL (Biological study)
(inhibition of, by BAY m 1099, blood sugar response to sulfonylurea and, in diabetic humans)

L64 ANSWER 81 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1985-050869 [09] WPIDS
DNC C1985-022178
TI Solid dosage forms of glibenclamid anti **diabetic** agent - comprising non-crystalline glibenclamid adsorbed on carrier.
DC A96 B05
IN HERRMANN, R; LAHR, W
PA (RENT) RENTSCHLER ARZNEIMITTEL
CYC 1
PI DE 3326167 A 19850221 (198509)* 22p
DE 3326167 C 19920917 (199238) 5p A61K031-64
ADT DE 3326167 A DE 1983-3326167 19830720; DE 3326167 C DE 1983-3326167 19830720
PRAI DE 1983-3326167 19830720
IC ICM A61K031-64
ICS A61K009-20; A61K047-00
AB DE 3326167 A UPAB: 19930925
Solid dosage forms of **glibenclamide**, i.e. 1-(4-(2-(5-chloro-2-methoxybenzamido) ethyl)phenylsulphonyl)- 3-cyclohexylurea (I), comprises non-crystalline (I) adsorbed on an inert insoluble carrier (II) and contained in capsules or pressed into tablets, opt. together with conventional additives. The (I):(II) **ratio** is 1:1-100, pref. 1:10-20 or esp. 1:3-10, and the residual solvent content of the adsorbate is less than 1wt.%.
USE/ADVANTAGE - (I) is used in the treatment of **diabetes**. The dosage forms give more rapid gastrointestinal absorption of (I) than known dosage forms (cf. DE 2355743 and 2348334) without instability problems or the need to use wetting agents.
0/0
FS CPI
FA AB
MC CPI: A04-D05; A12-V01; B04-C02; B04-C03; B05-B02C; B10-A08; B12-H05; B12-M11

L64 ANSWER 82 OF 92 MEDLINE
AN 85025830 MEDLINE
DN 85025830
TI Glyburide and glipizide, second-generation oral sulfonylurea hypoglycemic agents.
AU Prendergast B D
SO CLINICAL PHARMACY, (1984 Sep-Oct) 3 (5) 473-85. Ref: 80
Journal code: DKC. ISSN: 0278-2677.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 198502
AB The chemistry, pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and **dosage** of glyburide and glipizide, two second-generation oral sulfonylurea hypoglycemic agents, are reviewed.

Glyburide and glipizide are well absorbed after oral administration. The absorption of glipizide is delayed by food; in contrast, glyburide absorption does not seem to be affected by administration with meals. Both drugs are extensively metabolized by the liver. A two-compartment open model adequately describes the pharmacokinetics of these drugs. The apparent elimination half-life of glyburide in oral **dosage** forms available in the United States **ranges** from 7 to 10 hours. Glipizide has a terminal elimination half-life of 2-7 hours. The effects of renal and hepatic disease on the pharmacokinetics of glyburide and glipizide have not been well studied. Based on controlled, comparative studies in patients with new-onset, diet-failed, Type II diabetes, glyburide appears to be at least as effective as chlorpropamide and tolazamide in controlling blood glucose. Glipizide has shown efficacy comparable to or greater than that of chlorpropamide and tolbutamide. Glyburide and glipizide appear to be comparable in terms of their ability to control fasting blood glucose in Type II diabetics. The recommended initial **dosage** of glyburide in newly diagnosed Type II diabetics is 2.5-5 mg once daily. For glipizide, the initial **dosage** should be 5 mg once daily. Elderly or debilitated patients and those with renal or hepatic impairment should be started on **lower dosages** initially. Glyburide and glipizide have adverse effects that are similar to those observed with the first-generation oral hypoglycemic agents. Glyburide and glipizide do not appear to offer major therapeutic advantages over first-generation oral sulfonylurea hypoglycemic agents. However, they may represent therapeutic alternatives for some patients who do not respond satisfactorily to other sulfonylureas.

CT Check Tags: Comparative Study; Female; Human
Chemistry
Chlorpropamide: TU, therapeutic use
Costs and Cost Analysis
***Diabetes Mellitus: DT, drug therapy**
Diabetes Mellitus: ME, metabolism
Drug Therapy, Combination
Glipizide: AE, adverse effects
Glipizide: ME, metabolism
*Glipizide: TU, therapeutic use
Glyburide: AE, adverse effects
Glyburide: ME, metabolism
*Glyburide: TU, therapeutic use
Infant, Newborn
Insulin: TU, therapeutic use
Intestinal Absorption
Kidney Diseases: ME, metabolism
Kinetics
Liver Diseases: ME, metabolism
Pregnancy
Prenatal Exposure Delayed Effects
*Sulfonylurea Compounds: TU, therapeutic use
Tissue Distribution
Tolazamide: TU, therapeutic use
Tolbutamide: TU, therapeutic use

RN **10238-21-8 (Glyburide)**; 11061-68-0 (Insulin); 1156-19-0 (Tolazamide); 29094-61-9 (Glipizide); 64-77-7 (Tolbutamide); 94-20-2 (Chlorpropamide)

CN 0 (Sulfonylurea Compounds)

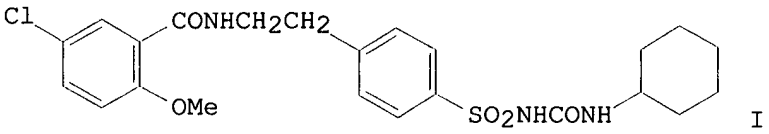
L64 ANSWER 83 OF 92 MEDLINE
AN 84237940 MEDLINE
DN 84237940
TI Hyperglycaemic clamp and insulin binding to isolated monocytes before and after glibenclamide treatment of mild type II diabetics.
AU Pagano G; Lombardi A; Pisu E; Bozzo C; Masciola P; Ferraris G M; Bruno A
SO HORMONE AND METABOLIC RESEARCH, (1984 May) 16 (5) 215-20.
Journal code: GBD. ISSN: 0018-5043.

CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198410
AB The therapeutic action of 3.5 mg glibenclamide (HB 420) once a day for six weeks was evaluated in ten mild NID diabetics previously treated with diet only. Stable HbA1, insulin secretion during hyperglycaemic clamp (100 mg/dl over the baseline in the first study, and at the same level in the second one), peripheral sensitivity expressed as the amount of dextrose infused per Kg per min (M-coefficient), the glucose metabolic clearance rate (MCR) and the M/I **ratio** were measured. Circulating monocytes were separated to assess insulin binding before and after treatment. The results included a significant decrease in HbA1 (7.5 +/- 0.3 against 8.4 +/- 0.4%, P less than 0.005), increased steady-state (100-120 min.) plasma insulin (31 +/- 4.4 against 25.7 +/- 3.9 microU/ml), a significant increase in M-coefficient (4.02 +/- 0.62 against 2.49 +/- 0.31 mg/Kg/min, P less than 0.01), and MCR (1.90 +/- 0.34 against 1.18 +/- 0.18 ml/Kg/min, P less than 0.025) and an increase in the M/I **ratio** (14.6 +/- 1.9 against 11.2 +/- 1.7). All subjects displayed an increase in total insulin binding (4.03 +/- 0.31% against 2.79 +/- 0.34%, P less than 0.001) and affinity constants (Ke = 8.3 +/- 0.6 against 6.6 +/- 0.4 X 10(7) M-1, P less than 0.05). Since the M/I **ratio** increased in only 7/10 subjects and since there was no significant correlations between the percentage increase in M and MCR and the plasma insulin increase, whereas the increase in R0 was significant, it is felt that the euglycaemizing action of **low doses** of glibenclamide is primarily peripheral.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Blood Glucose: ME, metabolism
Diabetes Mellitus, Non-Insulin-Dependent: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Diabetes Mellitus, Non-Insulin-Dependent: ME, metabolism
***Glucose: AD, administration & dosage**
Glyburide: PD, pharmacology
*Glyburide: TU, therapeutic use
Hemoglobin A, Glycosylated: AN, analysis
*Insulin: ME, metabolism
Insulin: SE, secretion
Metabolic Clearance Rate
Middle Age
*Monocytes: ME, metabolism
RN **10238-21-8 (Glyburide)**; 11061-68-0 (Insulin); 50-99-7 (Glucose)
CN 0 (Blood Glucose); 0 (Hemoglobin A, Glycosylated)

L64 ANSWER 84 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1983-790321 [42] WPIDS
DNC C1983-100134
TI Synergistic oral **antidiabetic** compsn. - contg. 5-aryl-oxazole-2,4-di one and hypoglycaemic sulphonyl urea compsn..
DC B03 B05
IN MORVILLE, M; PAGE, M G; SCHNUR, R C
PA (PFIZ) PFIZER INC
CYC 19
PI EP 91193 A 19831012 (198342)* EN 17p
R: AT BE CH DE FR GB IT LI LU NL SE
AU 8311897 A 19830908 (198343)
NO 8300685 A 19830926 (198345)
JP 58174321 A 19831013 (198347)
FI 8300653 A 19831031 (198350)
HU 28290 T 19831228 (198406)
ZA 8301354 A 19830926 (198406)
PT 76299 A 19840718 (198434)
CA 1194800 A 19851008 (198545)

EP 91193 B 19860521 (198621) EN
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3363577 G 19860626 (198627)
ADT EP 91193 A EP 1983-301044 19830228; ZA 8301354 A ZA 1983-1354 19830228
PRAI US 1982-353782 19820301; US 1982-450320 19821220
REP 2.Jnl.Ref; GB 2080803; GB 2083810; No-SR.Pub
IC A61K031-64; A61K045-06
AB EP 91193 A UPAB: 19930925
Oral **diabetic** compsn. consists of 5-aryloxyazol-2,4-dione of formula (I) together with one of the hypoglycaemic sulphonyl urea derivs. (B) chlorpropamide, tolbutamide, acetohexamide, tolazamide, glipizide or **glibenclamide** or their salts with bases. (where R is 3-thienyl, 4-ethoxy-3-thienyl, 2-fluorophenyl, 2-methoxyphenyl, 2-ethoxyphenyl, 2-methyl-5-fluorophenyl, 2-methoxy-5-fluorophenyl, 2-methoxy-6-fluorophenyl, 2-methoxy5-chlorophenyl, 2-methoxy-6-chlorophenyl, 2-methoxy-5-chloro-3-pyridyl or 2-ethoxy-5-chloro-3-pyridyl). The **ratio** of (I):(B) is in the **range** 1.0:0.2 to 1.0:2.0.
The combination is synergistic.
0/0
FS CPI
FA AB
MC CPI: B07-D06; B07-D10; B07-E01; B10-A08; B12-C09; B12-H05

L64 ANSWER 85 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:145918 HCAPLUS
DN 90:145918
TI Comparative effects of two **doses** of glibenclamide upon metabolic rhythms in maturity-onset diabetics
AU Nattrass, M.; Hinks, L.; Smythe, P.; Todd, P. G.; Alberti, K. G. M. M.
CS Fac. Med., Gen. Hosp., Southampton, Engl.
SO Diabete Metab. (1978), 4(3), 175-80
CODEN: DIMEDU; ISSN: 0338-1684
DT Journal
LA English
CC 1-6 (Pharmacodynamics)
GI



I

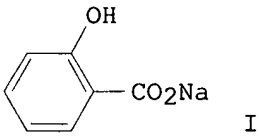
AB Five maturity-onset diabetics were studied during **therapy** with glibenclamide (I) [**10238-21-8**] (2.5 mg and 5 mg) by half-hourly blood sampling for 12 h. All patients had lower mean blood glucose concns. during **therapy** with 5 mg I. There was no significant difference between serum insulin [9004-10-8], concns. of the 2 **doses**, however, serum insulin/blood glucose **ratio** was higher during the larger **dose** of I. Mean blood lactate, pyruvate, and serum triglycerides were significantly lower, and blood glycerol, 3-hydroxybutyrate, and plasma nonesterified fatty acids were increased during **therapy** with 5 mg. In the individual patient the changes in blood glycerol and plasma nonesterified fatty acids were related to changes in circulating insulin concn. and did not appear to be a true extrapancreatic effect of I.
ST glibenclamide **diabetes** metabolic rhythm
IT **Diabetes** mellitus
(metabolic rhythm in, glibenclamide effect on)
IT Rhythm, biological
(diurnal, of metab. in **diabetes**, glibenclamide effect on)

IT **10238-21-8**
RL: BIOL (Biological study)
(metabolic rhythm response to, in **diabetes**)
IT 9004-10-8, biological studies
RL: BIOL (Biological study)
(release of, diurnal rhythm of, in **diabetes**, glibenclamide effect on)

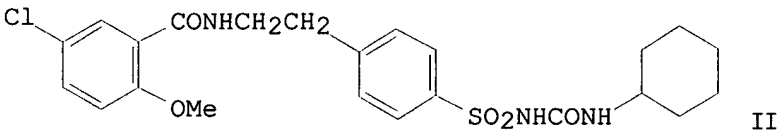
L64 ANSWER 86 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:595 HCAPLUS
DN 90:595
TI Biguanides and ketone body metabolism in animals and man
AU Alberti, K. G. M. M.; Holloway, P. A. H.; Johnson, G.; Man, K. C.; Nattrass, M.
CS Chem. Pathol. Hum. Metab., Gen. Hosp., Southampton, Engl.
SO Biochem. Clin. Aspects Ketone Body Metab., Int. Symp. (1978), Meeting Date 1976, 140-55. Editor(s): Soeling, Hans D.; Seufert, Claus D. Publisher: Thieme, Stuttgart, Ger.
CODEN: 38WNAA
DT Conference
LA English
CC 1-6 (Pharmacodynamics)
AB The use of phenformin [114-86-3] in normal **therapeutic doses** in stable maturity-onset diabetics resulted in increased circulating ketone body concns. with a marked increase in the 3-hydroxybutyrate [300-85-6]/acetoacetate [541-50-4] **ratio**. Effects were less marked with metformin [**657-24-9**]. Phenformin also increased blood ketone body concns. in normal and streptozotocin diabetic rats. In the isolated perfused fed rat liver, ketogenesis was increased by 60% by phenformin. In livers from starved rats, there was a **dose**-related inhibition of gluconeogenesis and stimulation of ketogenesis from lactate [50-21-5] by phenformin. Seventy to 80% of lactate could be accounted for as glucose [50-99-7] and ketone bodies, the data suggesting direct diversion of lactate to ketone bodies. There was no evidence the ketogenesis was increased through an increase in .beta.-oxidn. of fatty acids. Data from freeze-clamped livers suggested a block at the triose phosphate level, a lack of oxalacetate availability, and a more reduced intracellular state. Phenformin effects could be obsd. without a change in total hepatic ATP content. More direct information is required on the effects of biguanides on the intracellular disposition of ATP on the translocation of reducing equiv. across the mitochondrial membrane. These effects of biguanides on ketogenesis provide another reason for great circumspection in using them as hypoglycemic agents in man.
ST biguanide ketone body metab **diabetes**; phenformin ketone body metab **diabetes**; metformin ketone body metab **diabetes**
IT Hyperglycemia
(biguanide, ketone body metab. response to, in **diabetes**)
IT Liver, metabolism
(ketones body metab. by, metformin and phenformin effect on, in **diabetes**)
IT Ketone body
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, metformin and phenformin effect on, in **diabetes**)
IT **Diabetes** mellitus
(metformin and phenformin effect on ketone body metab. in)
IT Gluconeogenesis
(metformin and phenformin effect on, in **diabetes**)
IT 56-03-1D, derivs. 114-86-3 **657-24-9**
RL: BIOL (Biological study)
(ketone body metab. response to, in **diabetes**)
IT 50-21-5, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, by liver, phenformin effect on)

IT 50-99-7, biological studies 300-85-6 541-50-4, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, metformin and phenformin effect on, in **diabetes**)

L64 ANSWER 87 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:537529 HCAPLUS
DN 85:137529
TI Reexamination of the effect of salicylate on blood sugar and insulin levels in normal and diabetic subjects and possible repercussions on treatment with oral antidiabetics
AU Pitucco, Giovanni; Santucci, Anna; Caputo, Velia; De Mattia, Giancarlo; Federico, Michele
CS I Clin. Med. Gen. Ter. Med., Univ. Roma, Rome, Italy
SO Clin. Ter. (1976), 78(3), 227-44
CODEN: CLTEA4
DT Journal
LA Italian
CC 1-6 (Pharmacodynamics)
GI



I



II

AB In healthy subjects blood sugar and blood insulin [9004-10-8] concns. were affected only slightly and inconsistantly by infusion of Na salicylate (I) [54-21-7], but in diabetics I infusion lowered blood sugar and raised blood insulin. Similarly, the hypoglycemic and hyperinsulinemic effects of the oral antidiabetic glibenclamide (II) [**10238-21-8**] were little altered by I in the healthy persons but were potentiated by II in the diabetics. Simultaneous salicylate **therapy** with II may lead to better control of **diabetes** even with **lower doses** of II. Since the hypoglycemic and hyperinsulinemic effects of I, either alone or with II, were directly proportional to the initial hyperglycemia, there seems little danger of salicylates causing hypoglycemic accidents in diabetics.
ST salicylate **diabetes** blood sugar insulin; glibenclamide salicylate **diabetes**
IT **Diabetes** mellitus
(insulin and sugar of blood in, salicylate effect on, antidiabetic **therapy** in relation to)
IT Blood
(insulin of, salicylate effect on sugar and, in **diabetes**, antidiabetics **therapy** in relation to)
IT Blood sugar
(salicylate effect on insulin and, in **diabetes**, antidiabetic **therapy** in relation to)
IT 54-21-7
RL: BIOL (Biological study)
(blood insulin and sugar response to, in **diabetes**, antidiabetics **therapy** in relation to)
IT **10238-21-8**
RL: BIOL (Biological study)

(blood insulin and sugar response to, in **diabetes**, salicylate treatment in relation to)
IT 9004-10-8, biological studies
RL: BIOL (Biological study)
(of blood, salicylate effect on, in **diabetes**, antidiabetics **therapy** in relation to)

L64 ANSWER 88 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1971:508397 HCAPLUS
DN 75:108397
TI Advances in the treatment of **diabetes** with glibenclamide and phenformin
AU Beyer, J.; Ewald, W.; Kunkel, W.; Wolf, E.; Schoeffling, K.
CS Zentrum Inn. Med., Univ. Frankfurt/Main, Frankfurt/M., Ger.
SO Deut. Med. Wochenschr. (1971), 96(17), 728-33
CODEN: DMWOAX
DT Journal
LA German
CC 15 (Pharmacodynamics)
AB Glibenclamide (I) in **low doses** (mean 10.4 mg/24 hr) was markedly effective, esp. in treatment of secondary failures of sulfonylurea drugs. The secondary failure rate with I was 3-4% per patient per year. In case of secondary failure with I alone, addnl. phenformin improved the metabolic state and usually allowed continuation of oral antidiabetic treatment. I or I + phenformin administration led to a marked **redn.** in the daily insulin (II) **dose** with maintenance of body wt. in a large proportion of maturity-onset diabetics who had required II. In individual diabetics with a low II requirement further II could be dispensed with. On the other hand, the metabolic state of young diabetics with mild overwt. requiring II was not influenced by addnl. I administration.
ST phenformin glibenclamide **therapy diabetes**; insulin glibenclamide **therapy diabetes**; biguanide glibenclamide **therapy diabetes**
IT **Diabetes**
(glibenclamide and phenformin in treatment of)
IT 114-86-3
RL: BIOL (Biological study)
(**diabetes** treatment by glibenclamide and)
IT **10238-21-8**
RL: BIOL (Biological study)
(**diabetes** treatment by phenformin and)

L64 ANSWER 89 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1970:497111 HCAPLUS
DN 73:97111
TI Pharmacological studies with the hypoglycemic drug N-4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzeno sulfonyl-N'-cyclohexylurea (glybenclamide)
AU Dessi, Pietro
CS Ist. Farmacol. Ter. Sper., Univ. Bologna, Bologna, Italy
SO Acta Diabetol. Lat. (1969), 6(2), 206-21
CODEN: ADILAS
DT Journal
LA Italian/English
CC 15 (Pharmacodynamics)
AB The hypoglycemic activity of the title compd. was examd. by means of hypoglycemic **dose**/effect curves. The variations of the blood sugar levels in alloxan **diabetes**, the effect on liver glycogen in both fed and fasted dogs and rabbits, and toxicity were also studied. Hypoglycemia occurs at **doses** in the .mu.g/kg **range**. No activity occurs in alloxan **diabetes**. Liver glycogen undergoes diphasic glycogenolysis and neoglycogenesis. In acute toxicity expts. the LD50 is lower than that of other sulfonylurea drugs. With regard to the practical use of the drug, signs of chronic toxicity may not

be expected. No tertogenic effect occurs in rats even at repeated **doses** as high as 1/2 the LD50.
ST glybenclamide hypoglycemia **diabetes** glycogen; hypoglycemia **diabetes** glycogen glybenclamide; **diabetes** hypoglycemia glycogen glybenclamide; glycogen hypoglycemia **diabetes** glybenclamide
IT **10238-21-8**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pharmacology of)

L64 ANSWER 90 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1971:508423 HCAPLUS
DN 75:108423
TI Pharmacodynamics of HB 419
AU Schmidt, Felix Helmut; Stork, H.; Baender, A.; Pfaff, W.
CS Res. Lab., Boehringer Mannheim G.m.b.H., Mannheim-Waldhof, Ger.
SO HB 419 - New Oral Antidiabetic Drug, Pap. Symp. (1969), 25-33. Editor(s): Levine, Rachmiel. Publisher: Georg Thieme, Stuttgart, Ger.
CODEN: 23SWA5
DT Conference
LA English
CC 15 (Pharmacodynamics)
AB Hb 419 has a hypoglycemic effect on parenteral administration in human and in various species of animals in **doses ranging** from 5 to 10 .mu.g/kg. Blood glucose decreases 15-20 min after administration of Hb 419 with a species-related max. of 45-180 min. At the same time H 419 induces a redn. of the concn. of free fatty acids (FFA) in blood. Pharmacodynamically, HB 419 showed the same behavior as an injection of insulin, based on the reaction of the blood sugar and the FFA. HB 419 had no influence on the blood glucose in exptl. induced **diabetes** in the dog, rabbit, or rat. However, the concns. of FFA and hydroxybutyrate were reduced in alloxan-diabetic rass. HB 419 and similarly insulin induced a redn. of liver glycogen in the fed rat. Prolonged hypoglycemia in fasting rabbits and rats led to an increase in glycogen.
ST HB 419 pharmacodynamics; hypoglycemic HB 419
IT **Diabetes**
(fatty acids metabolism in alloxan, HB 419 effect on)
IT Hypoglycemia
(from HB 419)
IT Fatty acids, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabolism of, in **diabetes**, HB 419 effect on)
IT **10238-21-8**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pharmacology of)

L64 ANSWER 91 OF 92 HCAPLUS COPYRIGHT 2000 ACS
AN 1967:93938 HCAPLUS
DN 66:93938
TI Oral treatment of **diabetes** mellitus with drugs having various mechanisms of action
AU Berger, Willi; Constam, George R.
CS Med. Universitaetspoliklin., Zurich, Switz.
SO Schweiz. Med. Wochenschr. (1967), 97(14), 444-50
CODEN: SMWOAS
DT Journal
LA German
CC 15 (Pharmacodynamics)
AB The antidiabetic activities of sulfonylurea and pyrimidine derivs. and biguanides are discussed with regard to mode of action, side effects, and risk involved. For carbutamide, tolbutamide, and chlorpropamide, the max. maintenance **doses**/day in patients who were not under insulin treatment were **1.5**, 2.0, and 0.5 g., resp. Dimethylbiguanide was also effective. In patients under insulin

therapy, oral antidiabetics **reduced** the **dose** of insulin required for control. Without proper dietary control, oral hypoglycemic agents prematurely lost their effectiveness. 54 references.

ST **DIABETES** TREATMENT; DIMETHYLBIGUANIDE **DIABETES**; ANTIDIABETICS; TOLBUTAMIDE **DIABETES**; CARBUTAMIDE **DIABETES**; CHLORPROPAMIDE **DIABETES**

IT **Diabetes**
(carbutamide and chlorpropamide, in treatment of)

IT Diet
(in **diabetes** treatment with oral hypoglycemic agents)

IT Insulins, biological studies
(in dietary control, effect of carbutamide, chlorpropamide, etc., on)

IT 64-77-7 94-20-2 339-43-5 **657-24-9**
RL: BIOL (Biological study)
(in **diabetes** treatment, dietary control and)

L64 ANSWER 92 OF 92 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-108294 [10] WPIDS
DNC C2000-032735
TI Tablet comprising **metformin** and **glibenclamide** useful for the treatment of non-insulin dependent **diabetes**.
DC B05
IN BONHOMME, Y; NICHOLSON, G; CAVE, G; NICHOLSON, S J
PA (LIPH) LIPHA LYONNAISE IND PHARM
CYC 87
PI EP 974356 A1 20000126 (200010)* EN 8p A61K031-64
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
WO 2000003742 A2 20000127 (200013) EN A61K031-64
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
ADT EP 974356 A1 EP 1998-401781 19980715; WO 2000003742 A2 WO 1999-EP5571 19990712
PRAI EP 1998-401781 19980715
IC ICM A61K031-64
ICI A61K031-64, A61K031:155
AB EP 974356 A UPAB: 20000228
NOVELTY - A tablet comprises **metformin** (M) and **glibenclamide** (G), where the size of (G) is such that at most 10 % of the particles are less than 2 mu m and at most 10 % of the particles are greater than 60 mu m.
An INDEPENDENT CLAIM is also included for a tablet obtained by:
(a) forming granules by wet granulation of a mixture of (M) and (G);
(b) blending the granules with a tabletting aid; and
(c) tabletting the blend.
ACTIVITY - **Antidiabetic**.
USE - The tablets are useful for the treatment of non-insulin dependent **diabetes**.
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: B10-A08; B10-A17; B12-M11B; B14-S04